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Osteoarthritis (OA) is a disease of the total joint, not just the articular cartilage. The Osteoarthritis Research Society International Disease State Working Group defined OA as “a progressive disease representing the failed repair of joint damage that, in the preponderance of cases, has been triggered by abnormal intra-articular stress.” They noted that all tissues of the joint are involved, including not only the articular cartilage, but also the subchondral bone, ligaments, periarticular structures, and menisci, when present. The results of the OA process are cartilage degradation and bone remodeling; these features are associated with the development of symptoms of pain, stiffness, and functional disability. In this current concept of OA, the structural changes represent the disease while the symptoms of aching, discomfort, pain, and stiffness represent the illness for which patients seek medical care. This concept has profound implications for treatment: while there are drugs currently approved for treating the illness of OA, there are none currently approved for slowing the structural progression of OA.

Osteoarthritis (OA) is the most common form of arthritis, and is a major cause of morbidity, activity limitation, physical disability, excess health care utilization and reduced health-related quality of life, especially in people aged 45 and above in developed countries. The incidence (risk of developing the disease) and prevalence (proportion of persons with the disease) of OA increase with advancing age in both sexes. In general, women have a higher incidence and prevalence of symptomatic radiographic OA, particularly in the hands and knees. There are ethnic and racial differences in the occurrence of OA that may be due to genetic and/or lifestyle factors; these include the lower prevalence of hand and hip OA in Chinese and the higher prevalence of hip and knee OA in African Americans compared with whites.

It is now recognized that OA is not only a cause of pain and physical dysfunction, but is also associated with excess mortality. Losina and colleagues reported that the presence of knee OA, especially when combined with the presence of obesity, was associated with the loss of 3 to 4 quality-adjusted years of life. Neusch and colleagues, in analyzing data from a 15-year prospective cohort study in the United Kingdom, reported that persons with symptomatic hip and/or knee OA had a 50% increase in all-cause mortality compared with that expected based on their age and gender distribution. Risk factors for all-cause mortality included not only the presence of comorbid conditions such as cardiovascular disease, cancer, and diabetes, but also the presence of walking disability. This suggests that an approach to reducing walking disability in patients with symptomatic lower limb OA might not only improve quality of life, but also prolong survival.
Much research has focused on the role of obesity, joint injury, and genetic predisposition as risk factors for the development of OA. Metabolic syndrome—the phenotype characterized by abdominal obesity, dyslipidemia, hypertension, and type 2 diabetes mellitus due to insulin resistance—is associated with OA; this association may be mediated by the production of circulating adipokines and accumulation of age-related glycogen and products in articular cartilage. While the heritability of OA has been recognized for over 60 years, only in the past decade, with the development of commercially available genotyping platforms, have scientists been able to perform genome-wide association studies examining the association of single nucleotide polymorphisms (SNPs) with OA. The largest consortium to investigate the association of SNPs with radiographic and clinical OA is Translational Research in Europe, a global nucleotide polymorphisms (SNPs) with OA. The largest consortium to investigate the association of SNPs with radiographic and clinical OA is Translational Research in Europe Applied Technologies for OsteoArthritis (TreatOA); indeed, the TreatOA website (http://www.treatoa.eu/publications.html) currently lists more than 50 peer-reviewed articles on the results of genetic studies in OA.

The interplay between the articular cartilage and subchondral bone in the pathophysiology of OA has been increasingly recognized over the past decade and is a major focus for current research into the development and progression of OA. In early phases of OA, there are anabolic changes in both articular cartilage and subchondral bone. In the former, there is increased synthesis of matrix molecules while, in the latter, there is activation of the bone remodeling cycle. With progression of OA, catabolic changes dominate in the articular cartilage with increased synthesis of tissue-destructive enzymes including matrix metalloproteases (MMPs), and disintegrins and MMPs with thrombospondin motifs. Accompanying changes in the subchondral bone include trabecular thinning leading to relative osteopenia below areas of sclerosis due to thickening of the cortical plate. These changes are mediated, in part, by the diffusion of small molecules between bone and cartilage, including cytokines, angiogenic growth factors, and MMPs.

Another component of the OA process that has received increasing recognition is the role of synovitis. Studies have demonstrated increased expression of genes that encode cytokines (such as interleukin-1 and 15), chemokines, and MMPs in synovial fibroblasts. Synovitis, as measured on magnetic resonance imaging (MRI) and/or ultrasound, is associated with both pain and structural progression; it is not known, however, whether specific anti-inflammatory therapy is more efficacious in patients with synovitis than in those without it.

Synovitis is but one feature of OA that is associated with pain; others include the presence of moderate-to-large bone marrow lesions and joint effusions. Studies of the mechanisms of pain in OA have increasingly explored the nature of OA pain and the role of peripheral and central sensitization superimposed on peripheral nociception. Peripheral sensitization has a spinal component with signal amplification in neurons of the spinal cord underlying both primary and secondary hyperalgesia. In addition, there is central sensitization, manifested by lower pressure pain thresholds and higher pain summation scores. The mechanisms of central sensitization in OA may be due to spinal hyperexcitability coupled with defective descending inhibitory noxious control pathways. Functional MRI studies in patients with chronic OA pain have demonstrated atrophy in the thalamus and gray matter of pain-related cortical areas, which is partially reversible after total joint arthroplasty.

The management of patients with OA continues to evolve with more evidence supporting the efficacy of nonpharmacologic modalities as well as the approval and study of newer pharmacological modalities, including biologic agents. The American College of Rheumatology published new recommendations for the medical management of OA of the hand, hip, and knee in 2012. Nonsteroidal anti-inflammatory drugs (NSAIDs) remain the cornerstone of oral therapy for pain in patients with OA, despite their association with potential serious adverse events including gastrointestinal bleeding from complicated ulcers and small and large bowel lesions, and cardiovascular thrombotic events, especially myocardial infarction. Patients who have an inadequate response to or are unable to tolerate oral NSAIDs may be treated with intra-articular agents such as glucocorticoids and hyaluronates and/or centrally acting analgesics such as tramadol, duloxetine, and opioids. The efficacy of duloxetine—a serotonin norepinephrine reuptake inhibitor that can be used either alone or as an adjunct to acetaminophen or NSAIDs—supports the observations summarized above that demonstrate the role of central sensitization in chronic OA pain due to loss of diffuse inhibitory noxious control.

There remains an unmet need for both more efficacious treatments for pain and agents that are capable of modifying the rate of structural progression in OA. Tanezumab, a monoclonal antibody directed against nerve growth factor, has demonstrated efficacy in patients with hip and knee OA with moderate to severe pain. However, the development of this agent, and of other compounds in its class, has been placed under clinical hold by the US Food and Drug Administration (FDA) because of reports of osteonecrosis adverse events that were eventually adjudicated to be rapidly destructive OA involving not only index joints such as the hip and knee, but also non-index joints such as the shoulder. Further studies of the mech-
anism underlying these joint-related serious adverse events are needed to assess the risk-benefit relationship of this promising treatment for pain in patients with OA.

There have been many studies involving potential disease-modifying OA drugs (DMOADs); however, there are no agents that are approved at this time by either the FDA or European Medicines Agency (EMA) for this indication. Recent data suggest that oral strontium ranelate, at doses of either 1 or 2 g per day, significantly reduced the rate of decline in joint space width compared with placebo in subjects with knee OA followed for a mean of 30 months. Similar results were noted when subjects were classified as “progressors” based on a decline in joint space width of at least 0.5 mm. Another approach to disease modification is the application of principles of regenerative medicine with endogenous stem cells. It is hoped that the results of basic biomedical, clinical, and translational research will provide new approaches to the management of patients with OA during the remaining years of this and future decades.

References

Keywords: osteoarthritis, pathophysiology, risk factors, treatment
ÉDITORIAL

Dans les phases précoces de l’arthrose, des changements anaboliques interviennent aussi bien dans le cartilage articulaire que dans l’os sous-chondral. Dans le premier type de tissu se produit une augmentation de la synthèse des molécules de la matrice tandis que dans le second se déroule une activation du cycle du remodelage osseux. Au fur et à mesure de la progression de l’arthrose, les changements cataboliques dominent dans le cartilage articulaire, avec une augmentation de la synthèse d’enzymes destructrices des tissus.”

Arthrose : nouvelles approches

par M. C. Hochberg, États-Unis

L’arthrose est une maladie qui affecte la totalité de l’articulation, et non pas seulement le cartilage articulaire. Le Groupe de travail de l’OARSI (Osteoarthritis Research Society International, la Société internationale de recherche sur l’arthrose) a défini l’arthrose de la façon suivante : « maladie progressive correspondant à une incapacité de réparation des lésions articulaires qui, dans la majorité des cas, ont été déclenchées par des stress intra-articulaires anormaux ». Il a été observé que tous les tissus de l’articulation sont touchés, non seulement le cartilage articulaire, mais également l’os sous-chondral, les ligaments, les structures péritarticulaires et les ménisques lorsqu’ils sont présents. Le processus arthrosique conduit à une dégradation du cartilage et à un remodelage osseux ; ces caractéristiques sont associées au développement de symptômes douloureux, de raideur et d’incapacité fonctionnelle. Dans ce concept actuel de l’arthrose, les altérations structurelles représentent la maladie, tandis que les symptômes à type de douleur sourde, gêne, douleur et raideur constituent la pathologie pour laquelle les patients consultent un médecin. Ce concept a d’importantes répercussions sur le traitement : alors que certains médicaments sont actuellement autorisés pour le traitement de la pathologie de l’arthrose, il n’existe actuellement aucun traitement approuvé ralentissant la progression structurelle de l’arthrose.

L’arthrose, la forme la plus fréquente d’arthropathie, est une cause importante de morbidité, de limitation des activités, d’incapacité physique, de surutilisation des soins de santé et de réduction de la qualité de vie liée à la santé, et ce plus particulièrement chez les personnes âgées de 45 ans et plus dans les pays développés. L’incidence (le risque de développer la maladie) et la prévalence (proportion de personnes atteintes de la maladie) de l’arthrose augmentent avec l’âge dans les deux sexes. D’une manière générale, les femmes présentent une incidence et une prévalence supérieures d’arthrose symptomatique radiographique, en particulier au niveau des mains et des genoux. Il existe des différences ethniques et raciales dans la surve- nue de l’arthrose, principalement liées à des facteurs génétiques et/ou relatifs au style de vie ; notamment une prévalence plus faible de l’arthrose des mains et de la hanche chez les Chinois, et une prévalence supérieure de l’arthrose de la hanche et du genou chez les Afro-Américains par rapport aux blancs.

Il est désormais établi que l’arthrose provoque non seulement une douleur et un dysfonctionnement physique, mais qu’elle est également associée à un excès de mortalité. Losina et coll. ont indiqué que la présence d’une arthrose du genou, en particulier en cas d’obésité concomitante, était associée à une perte de 3 à 4 années de vie ajustées sur la qualité de vie. Neusch et coll., qui ont analysé les don-
nées d’une étude de cohorte prospective de 15 ans menée au Royaume-Uni, ont montré que les personnes présentant une arthrose symptomatique de la hanche et/ou du genou présentaient une augmentation de 50 % de la mortalité de toute cause par rapport à celle prévue sur la base d’une distribution par tranche d’âge et sexe.1 Les facteurs de risque de mortalité de toute cause comprennent la présence de comorbidités, notamment les maladies cardio-vasculaires, le cancer et le diabète, mais également la présence d’une incapacité à la marche. Cela suggère qu’une approche permettant de réduire l’incapacité à la marche chez les patients atteints d’arthrose symptomatique des membres inférieurs pourrait non seulement améliorer leur qualité de vie, mais également prolonger leur durée de vie.

Un grand nombre de recherches ont porté sur le rôle de l’obésité, des lésions articulaires et de la prédisposition génétique comme facteurs de risque du développement de l’arthrose.7-8 Le syndrome métabolique – un phénomène caractérisé par une obésité abdominale, une dyslipidémie, une hypertension et un diabète de type 2 dû à une insulinorésistance – est associé à l’arthrose ; cette association pourrait être due à la production d’adipokines circulantes et l’accumulation de produits terminaux de glycation liés à l’âge dans le cartilage articulaire.9 La transmission héréditaire de l’arthrose est reconnue de manière généralisée.10-11 Dans les phases précoces de l’arthrose, des changements cataboliques dominent dans le cartilage articulaire, avec une augmentation de la synthèse d’enzymes destructrices des tissus, notamment les métalloprotéinases de la matrice (MMP), ainsi que des désintégrines et des MMP mu- nies de motifs thrombospondines. Les changements concor- mitant dans l’os sous-chondral comprennent un amincisse- ment trabéculaire provoquant une ostéopenie relative sous les zones de scérrose, liée à l’épaississement de la plaque cor- ticale. Ces changements sont assurés en partie par la diffu- sion de petites molécules entre l’os et le cartilage, notamment des cytokines, des facteurs de croissance angiogéniques et des MMP.

Un autre composant du processus arthrosique de mieux en mieux identifié est le rôle de la synovite.12,13 Des études ont démontré une augmentation de l’expression des gènes co- dant pour les cytokines (notamment les interleukines 1 et 15), les chimiokines et les MMP dans les fibroblastes synoviaux. La synovite, mesurée par imagerie par résonance magnétique (IRM) et/ou échographie, est associée à la fois à la présence de douleurs et à une progression structurelle ; il n’a cepen- dant pas été établi si un traitement anti-inflammatoire spécé- fique était plus efficace chez les patients atteints de syno- vite que chez ceux qui ne l’étaient pas.

La synovite est l’une des caractéristiques de l’arthrose as- sociée à la douleur ; les autres comprennent la présence de lésions modérées à importantes de la moelle osseuse et d’épanchements articulaires. Les études des mécanismes de la douleur dans l’arthrose explorent de plus en plus souvent la nature de la douleur arthrosique et le rôle de la sensibilisa- tion périphérique et centrale associée à la nociception péri- phérique.14,15 La sensibilisation périphérique a une compo- sante rachidienne s’accompagnant d’une amplification des signaux dans les neurones de la moelle épinière, qui sous-tend une hyperalgie primitive et secondaire. En outre, il existe une sensibilisation centrale, qui se manifeste par l’abaissement des seuils de douleur à la pression et une augmentation des scores totaux de douleur. Les mécanismes de la sensibilisa- tion centrale dans l’arthrose peuvent être dus à une hyperex- citabilité rachidienne couplée à un déficit des voies de contrôle descendantes inhibitrices des stimuli nociceptifs. Des études d’IRM fonctionnelle menées chez des patients présentant une douleur arthrosique chronique ont mis en évidence l’atrophie des zones corticales liées à la douleur dans le thalamus et la substance grise, partiellement réversible après une arthroplas- tie articulaire totale.

La prise en charge des patients atteints d’arthrose ne cesse d’évoluer au fur et à mesure que les preuves confirmant l’ef- ficacité des modalités non pharmacoépidémiologiques s’ac-
cumulent, mais également avec l’autorisation de nouvelles modalités pharmacologiques, notamment les agents biologiques, et les études qui sont menées dessus.16 L’Académie américaine de rhumatologie (American College of Rheumatology) a publié en 2012 de nouvelles recommandations sur la prise en charge médicale de l’arthrose de la main, de la hanche et du genou.17 Les anti-inflammatoires non stéroïdiens (AINS) restent la base du traitement oral de la douleur chez les patients arthrosiques, malgré leur association à des effets indésirables potentiellement graves, notamment des hémorragies gastro-intestinales provenant d’ulcères compliqués et de lésions de l’intestin grêle et du gros intestin, ainsi que des événements cardio-vasculaires thrombotiques, en particulier l’infarctus du myocarde. Les patients présentant une réponse inadéquate ou n’étant pas en mesure de tolérer les AINS oraux peuvent être traités par des agents intra-articulaires, notamment les glucocorticoides et les hyaluronates et/ou des analgésiques centraux, par exemple le tramadol, la duloxétine et les opiacés. L’efficacité de la duloxétine – un inhibiteur de la recapture de la sérotonine et de la noradrénaline pouvant être utilisé seul ou en complément du paracétamol ou des AINS – confirme les observations résumées ci-dessus, démontrant le rôle de la sensibilisation centrale dans la douleur arthrosique chronique provoquée par la perte du contrôle inhibiteur diffus induit par la nociception.

Il reste sur ce plan un besoin non satisfait de traitements plus efficaces de la douleur et d’agents capables de modifier la vitesse de progression structurelle de l’arthrose. Le tanézumab, un anticorps monoclonal dirigé contre le facteur de croissance nerveuse, a démontré son efficacité chez les patients atteints d’arthrose de la hanche et du genou présentant une douleur modérée à sévère.18 Cependant, le développement de cet agent et des autres composés de sa classe a fait l’objet d’une suspension clinique de la part de la Food and Drug Administration (FDA), à cause d’événements indésirables à type d’ostéonécrose finalement confirmés comme constituant une arthrose rapidement destructrice affectant non seulement les articulations de référence comme la hanche et le genou, mais également d’autres articulations, notamment l’épaule. D’autres études sur le mécanisme lié à ces événements indésirables articulaires graves sont nécessaires pour évaluer le rapport bénéfice-risque de ces traitements prometteurs de la douleur chez les patients atteints d’arthrose.

De nombreuses études ont été menées sur les traitements de fond de l’arthrose ; cependant, aucun médicament n’a jusqu’à présent été approuvé par la FDA ou l’Agence européenne des médicaments (EMA) dans cette indication. De récentes données suggèrent que le ranélate de strontium par voie orale, à des posologies de 1 ou 2 g par jour, réduit de manière significative le taux de décim de l’épaisseur de l’interligne articulaire par rapport à un placebo chez des sujets présentant une arthrose du genou suivis pendant une durée moyenne de 30 mois.19 Des résultats similaires ont été recueillis lorsque les sujets ont été classés comme « progresseurs » sur la base d’une diminution de l’interligne articulaire d’au moins 0,5 mm.20 Une autre approche de l’évolution de la maladie est l’application des principes de la médecine régénérative avec des cellules souches endogènes.21 Les résultats de recherches biomédicales fondamentales, cliniques et translationnelles suscitent l’espoir de fournir de nouvelles approches pour la prise en charge des patients atteints d’arthrose vers la fin de cette décennie et dans les décennies à venir.□
Epidemiology of osteoarthritis

by C. Cooper, E. Dennison, M. Edwards, and A. Litwic, United Kingdom

Osteoarthritis is a global degenerative joint disease involving the cartilage and many of its surrounding tissues. Prevalence and incidence estimates of osteoarthritis in different populations may vary considerably due to different diagnostic classifications; in general, radiographic case definition produces the highest estimates, with self-reported and symptomatic osteoarthritis definitions producing similar estimates. The World Health Organization’s Scientific Group on Rheumatic Diseases estimates that 10% of the world’s population aged 60 years or older have significant clinical problems that could be attributed to osteoarthritis. The highest osteoarthritis prevalence estimates are found in the hand joints, with women more commonly affected than men.

Definition and classification

Osteoarthritis (OA) is a degenerative joint disease involving the cartilage and many of its surrounding tissues. In addition to damage and loss of articular cartilage, there is remodeling of subarticular bone, osteophyte formation, ligamentous laxity, weakening of periarticular muscles, and, in some cases, synovial inflammation. These changes may occur as a result of an imbalance in the equilibrium between the breakdown and repair of joint tissue. Primary symptoms of OA include joint pain, stiffness, and limitation of movement. Disease progression is usually slow but can ultimately lead to joint failure with pain and disability.

There have been many attempts to accurately identify and grade radiographic disease in OA. Of these, the classification by Kellgren and Lawrence (K&L) is the most widely accepted and used. Overall, grades of severity are determined from 0 to 4 and are related to the presumed sequential appearance of osteophytes, joint space loss, sclerosis, and cysts. The World Health Organization (WHO) adopted these criteria as the standard for epidemiological studies on OA. Cross-sectional imaging methods, such as magnetic resonance imaging (MRI), can visualize joint structures in more detail and continue to undergo evaluation to determine if they will provide a means by which the definition of OA can be refined.

Many studies now report the prevalence of self-reported or symptomatic OA; these differing approaches may go some way toward explaining part of the heterogeneity in OA estimates. A recent systematic review attempted to understand the differences in prevalence and incidence of OA according to case definition in knee, hip,
and hand joints and concluded that radiographic case definition afforded the highest estimates, while self-reported and symptomatic OA definitions presented similar estimates. The interrelationship between the different classifications used is shown in Figure 1.

**Epidemiology**

OA may develop in any joint, but most commonly affects the knee, hip, hand, spine, and foot. In 2005, it was estimated that over 26 million people in the USA had some form of OA. In a study from the Netherlands, 75% of women aged between 60 and 70 years had evidence of OA in the distal interphalangeal (DIP) joints, and 10% to 20% of subjects aged below 40 years were reported to have OA radiological changes in their hands or feet. In a rural sample from the former Soviet Republic of Turkmenia, all males over the age of 65 years had at least one affected hand joint. Symptomatic hand OA, as defined by the American College of Rheumatology (ACR) criteria, is, however, far less common. Its prevalence was found to be 8% in the US National Health and Nutrition Examination Survey (NHANES III). Data from the Framingham cohort demonstrated a prevalence of 13.2% in men and 26.2% in women aged ≥70 years, with at least one hand joint with symptomatic OA. A study from Teheran showed that the prevalence of hand OA in people aged 40 to 50 years was 2.2%, rising with age to 22.5% in people aged >70 years. As with many studies, including the Framingham cohort, differentiation by sex in this population showed that women were more frequently affected than men. Epidemiology of osteoarthritis – Cooper and others

** SELECTED ABBREVIATIONS AND ACRONYMS **

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<td>COPCORD</td>
<td>Community Oriented Program for the Control of Rheumatic Disorders</td>
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<tr>
<td>DIP</td>
<td>distal interphalangeal</td>
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<tr>
<td>NHANES</td>
<td>National Health And Nutrition Examination Survey</td>
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<tr>
<td>OA</td>
<td>osteoarthritis</td>
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<td>WHO</td>
<td>World Health Organization</td>
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The prevalence of radiographic hand OA varies greatly and has been reported to range from 27% to over 80%. In a study from the Netherlands, 75% of women aged between 60 and 70 years had evidence of OA in the distal interphalangeal (DIP) joints, and 10% to 20% of subjects aged below 40 years were reported to have OA radiological changes in their hands or feet. In a rural sample from the former Soviet Republic of Turkmenia, all males over the age of 65 years had at least one affected hand joint. Symptomatic hand OA, as defined by the American College of Rheumatology (ACR) criteria, is, however, far less common. Its prevalence was found to be 8% in the US National Health and Nutrition Examination Survey (NHANES III). Data from the Framingham cohort demonstrated a prevalence of 13.2% in men and 26.2% in women aged ≥70 years, with at least one hand joint with symptomatic OA. A study from Teheran showed that the prevalence of hand OA in people aged 40 to 50 years was 2.2%, rising with age to 22.5% in people aged >70 years. As with many studies, including the Framingham cohort, differentiation by sex in this population showed that women were more frequently affected than men. Epidemiology of osteoarthritis – Cooper and others

** Figure 1. ** Relationships between osteoarthritis (OA) classifications. After reference 3: Pereira et al. 2011;19:1270-1285. © 2011, Elsevier Ltd.

Knee OA

Knee involvement occurs less frequently than hand OA, although, similarly, it is more common in women, with female-to-male ratios varying between 1.5:1 and 4:1. Prevalence rates for knee OA, based on population studies in the USA, are comparable to those in Europe. These studies report that severe radiographic changes affect 1% of people aged between 25 and 34 years and this figure increases to nearly 50% in those 75 years and above.14 Few studies have reported secular trends in knee pain; a recent report from the Framingham Study found that the age- and BMI-adjusted prevalence of knee pain and symptomatic knee OA approximately doubled in women and tripled in men over 20 years (Figure 3, page 148); no such trend was observed in the prevalence of radiographic knee OA.15 Similarly, using questionnaire data enquiring about pain in and around the knee, the same researchers found that the age- and BMI-adjusted prevalence of knee pain increased by about 65% in NHANES from 1974 to 1994 among non-Hispanic white and Mexican American men and women and among African American women.15 These secular trends could not be fully explained by increasing obesity. According to data produced by the Dutch Institute for Public Health, the prevalence of knee OA in those aged 55 and above was 15.6% in men and 30.5% in women.7 Geographical variation in OA epidemiology also exists. Studies from China, which used similar methods and definitions to those used in the Framingham Study, found that the prevalence of bilateral knee OA and lateral compartment disease were two to three times higher in Chinese cohorts compared with estimates from the Framingham OA Study.16 Data on clinically diagnosed knee OA in the Community Oriented Program for the Control of Rheumatic Disorders studies (COPCORD) in Asia showed that the prevalence within this area ranged from 1.4% in urban Filipinos to 19.3% in rural communities in Iran.17 Part of the reason for this difference may be explained by the physical and socioeconomic environment. The COPCORD studies conducted in India, Bangladesh, and Pakistan looked specifically into differences between rural and urban populations. In India, it showed a significantly higher prevalence of
knee pain in rural (13.0%) than in urban (8.1%) communities. Furthermore, in China, men aged 60 years and above from a rural community had approximately double the prevalence of symptomatic knee OA than their urban counterparts.

**Hip OA**

Hip OA is less common than either hand or knee OA. The mean prevalence of primary radiographic hip OA in studies from Asia and Africa is 1.4% and 2.8%, respectively. These levels are much lower than those seen in Europe and North America. In the Study of Osteoporotic Fractures, the prevalence of radiographic hip OA was analyzed in women over the age of 65, using eleven different definitions. Excluding the definition of minimum joint space of less than 2.5 mm, the prevalence ranged from 1.0% to 6.2%, depending on the definition used.

**Risk factors**

OA is referred to as “primary” in the absence of an extrinsic cause. The proportion of individuals with primary OA within a specific OA population varies greatly. As age increases, the likelihood of an individual having primary OA increases. There are also differences by sex; in the Queensland Aboriginal communities it was found that 88% of women had primary OA, whereas 82% of men had secondary OA.

The risk of developing OA is determined by both systemic and local factors. Several systemic factors have been identified; these may act by increasing the susceptibility of the joints to injury, by direct damage to joint tissues, or by impairing the process of repair in damaged joint tissue. Local factors are most commonly biomechanical in nature and adversely affect the forces applied to the joint. Risk factors are discussed individually below; the varying prevalence of some, such as obesity and nutritional factors, may partly explain the differing rates of OA seen in different populations.

**Age**

The prevalence and incidence of radiographic and symptomatic OA considerably increase with age. The relationship between age and the risk of OA is likely multifactorial and is probably the consequence of numerous individual factors that may include oxidative damage, thinning of cartilage, muscle weakening, and a reduction in proprioception. Furthermore, the basic cellular mechanisms that maintain tissue homeostasis decline with age, leading to an inadequate response to stress or joint injury and resultant joint tissue destruction and loss.

**Sex**

The incidence of knee, hip, and hand OA is higher in women than men and in women it increases dramatically around the time of menopause. The latter finding has led investigators to hypothesize that hormonal factors may play a role in the development of OA, but the results of clinical and epidemiologic studies have not universally corroborated this. A recent systematic review of 17 studies found that there was no clear association between sex hormones and hand, knee, or hip OA in women, although single analysis of the studies was not possible due to study heterogeneity.

**Ethnicity and race**

The prevalence of OA and patterns of joint involvement vary among different racial and ethnic groups. Both hip and hand OA were much less frequent among Chinese in the Beijing Osteoarthritis Study than in whites in the Framingham Study, but interestingly, Chinese women had a higher prevalence of knee OA, which may be explained by excessive knee loading from squatting. Indeed, prolonged squatting and kneeling has been associated with an increased risk of moderate to severe radiographic knee OA. Results from the Johnston County Osteoarthritis Project have shown that the prevalence of hip OA in African American women was similar to that in white women, but that the prevalence was slightly higher in African American men (21%) than in white men (17%).

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Smoking may be associated with a greater risk of both cartilage loss and knee pain in OA. A recent meta-analysis of observational studies concluded that the observed protective effect of smoking in OA is likely to be false. It may be caused by selection bias, as many studies have been conducted in a hospital setting where control subjects have smoking-related conditions, and subjects were recruited as part of studies that were not primarily designed to investigate smoking.

Genetics
Strong evidence from family clustering and twin studies indicates that the risk of OA has an inherited component. Classic twin studies have shown that the influence of genetic factors is between 39% and 65% in radiographic OA of the hand and knee in women, about 60% in OA of the hip, and about 70% in OA of the spine. Although specific genes have been identified, the individual effects are relatively small; for example, Kerkhof et al. reported a genome-wide association study showing that the C allele of rs3815148 on chromosome 7q22 was associated with a 1.14-fold increased prevalence of knee and/or hand OA and also with a 30% increased risk of knee OA progression.

Nutrition (including vitamin D)
Dietary factors are the subject of considerable interest in OA. Protection against knee OA progression has been reported in older men and women with high dietary vitamin D intakes, and for those with high serum levels of vitamin D. The Rotterdam Study reported that low vitamin D intake increased the risk of progression of knee OA. The Osteoporotic Fractures in Men study found that men with vitamin D deficiency were twice as likely to have prevalent radiographic OA, but a recent longitudinal study of Finnish participants failed to find associations between low vitamin D status and risk of incident hip or knee OA. Although the results are inconsistent, a biologically plausible mechanism for the effect of vitamin D on OA could be postulated, through its important role in bone metabolism, which may modulate periarticular bone responses to excess loading and joint damage. The results of further studies are awaited.

Low vitamin C dietary intake has also been associated with an increased risk of OA progression among participants in the Framingham Study. A role for selenium has also been postulated.

Osteoporosis
Osteoporosis is, like OA, a common age-related skeletal disorder. While early results indicated that reduced bone mineral density might be protective against OA, further studies have been inconsistent with this finding. A systematic review and meta-analysis of the risk factors for the onset of knee OA in older adults has shown that there is a consistent strong association between increased bone mineral density and the onset of knee OA in the three studies that investigated this risk factor in women. Although a definite molecular basis and common pathophysiology have not been identified to explain the inverse relationship between OA and osteoporosis, a shared genetic component may explain why they seldom coexist.

Smoking
There have been conflicting reports on the role of smoking in OA. Some studies have reported a protective association between smoking and OA, but others in contrast, report that smoking may be associated with a greater risk of both cartilage loss and knee pain in OA. A recent meta-analysis of observational studies concluded that the observed protective effect of smoking in OA is likely to be false. It may be caused by selection bias, as many studies have been conducted in a hospital setting where control subjects have smoking-related conditions, and subjects were recruited as part of studies that were not primarily designed to investigate smoking.
quently increased OA risk. This risk is greater still if the subject has OA in another joint. The repetitive and excessive joint loading that accompanies specific physical activities increases the risk of developing OA in the involved joints. Workers whose jobs require repeated pincer grip have an increased loading that accompanies specific physical activities in another joint. The repetitive and excessive joint loading increases the OA risk. This risk is greater still if the subject has OA in another joint. The repetitive and excessive joint loading that accompanies specific physical activities increases the risk of developing OA in the involved joints. Workers whose jobs require repeated pincer grip have an increased loading that accompanies specific physical activities.

There have been conflicting results in studies examining the relationship between sporting activities and subsequent OA. There is some evidence that elite long-distance runners are at high risk of developing knee and hip OA. Other studies suggest that in the absence of joint injury, moderate recreational running and sports participation do not appear to increase the risk of hip or knee OA. The mechanical alignment of the knee influences load distribution across the articular surfaces. In a normally aligned knee, 60% to 70% of the weight-bearing load is transmitted through the medial compartment. Any shift in either a valgus or varus direction affects load distribution. Abnormal increases in compartmental loading are thought to increase stress on the articular cartilage—and other joint structures—subsequently leading to degenerative change. A systematic review has confirmed that knee malalignment is an independent risk factor for the progression of knee OA.

**Conclusion**

OA is the commonest joint disease worldwide and mainly occurs in later life. It tends to be slowly progressive and can cause significant pain and disability. Symptoms and radiographic changes are poorly correlated and thus defining OA for research purposes is challenging. Established risk factors include obesity, local trauma, and occupation. These, in addition to genetic factors, may partly explain geographic variations in OA prevalence. There is conflicting evidence regarding the roles of nutrition, smoking, and sarcopenia, with the results of further studies awaited.

**References**


**Keywords:** burden; epidemiology; osteoarthritis; risk factor

### ÉPIDÉMIOLOGIE DE L’ARTHROSE

L’arthrose est une maladie dégénérative articulaire mondiale touchant le cartilage et la plupart des tissus environnants. Sa prévalence et son incidence varient considérablement d’une population à l’autre selon les classifications diagnostiques utilisées pour les estimer; la définition radiologique de l’arthrose donne généralement les estimations les plus élevées, tandis que les définitions symptomatiques et auto-rapportées donnent des estimations à peu près équivalentes entre elles. D’après le groupe scientifique des maladies rhumatologiques de l’OMS, 10% des gens âgés de 60 ans ou plus ont des problèmes cliniques significatifs pouvant être attribués à l’arthrose. L’arthrose a une plus forte prévalence au niveau des articulations de la main, et touche plus volontiers les femmes que les hommes.
Osteoarthritis (OA) is the most common disorder of the musculoskeletal system and the leading cause of functional incapacity and disability in adults. A significant number of studies have demonstrated that patients with OA are at significantly higher risk of developing comorbid conditions than people without the disease. OA is most commonly associated with cardiovascular diseases, including arterial hypertension, as well as obesity, diabetes mellitus, and pulmonary diseases. The combination of various chronic diseases with diseases of the musculoskeletal system, especially with OA, will be observed more and more frequently, and will affect not only health care systems, but also the quality of life. The relation between OA and comorbid disorders may be explained, to some extent, by common etiologic and pathogenetic mechanisms, or may be related to the biological processes of aging, which can lead not only to the development, but possibly also to the maintenance of comorbidities. The data presented in this article suggest that OA is a disease that is pathogenetically related to cardiovascular diseases, obesity, and other metabolic conditions. As a consequence, the examination of OA patients should not be limited to the assessment of their articular disorder, but rather should be comprehensive, with particular attention paid to the state of their cardiovascular system. This article highlights the importance of using an integrated approach when considering treatment options.

risk of death was higher in the presence of radiographic evidence of OA of the distal interphalangeal joints of both hands. Although there is a discrepancy between the presence of pain and the radiographic signs of OA, which are observed together in 15% to 76% of cases, higher mortality rates are found both in patients with symptomatic OA and in those with only radiographic evidence of the disease. This suggests that OA is not only the most common disease of the joints, but also the most urgent problem in general practice. Osteoarthritis— along with cardiovascular diseases (CVD), degenerative diseases of the nervous system, and osteoporosis—is an age-related disorder. Moreover, joint dysfunction and pain and the resulting reduction in physical activity are destabilizing factors in the course of various somatic disorders. In patients with underestimated concomitant somatic diseases, OA is associated with a high rate of drug-related complications, especially when nonsteroidal anti-inflammatory drugs (NSAIDs) are used.

Many studies have demonstrated that patients with OA are at significantly higher risk of developing comorbid conditions than people without the disease. In their 18-month follow-up study of 1026 patients with OA, Kadam et al revealed a clear correlation between the number of concomitant conditions ("morbidity count") and a patient’s physical function. Almost half of the patients with OA (49%) were diagnosed with more than 5 conditions other than OA (high morbidity count); 28% had 3 or 4 conditions (medium morbidity count), 25% had 1 or 2 conditions (low morbidity count), and only 3.7% of the patients had OA alone. In osteoarthritic patients, high morbidity counts were associated with reduced physical function. Almost one half of the patients with OA (49%) were diagnosed with more than 5 conditions other than OA (high morbidity count); 28% had 3 or 4 conditions (medium morbidity count), 25% had 1 or 2 conditions (low morbidity count), and only 3.7% of the patients had OA alone. In osteoarthritic patients, high morbidity counts were associated with reduced physical function (after adjusting for age, sex, and socioeconomic parameters).

**Osteoarthritis and cardiovascular disease**

OA is most commonly associated with CVD, including arterial hypertension (AH), as well as obesity, diabetes mellitus, and pulmonary diseases. An analysis of publications in Medline in the period from 1966 to July 2004 revealed that hypertension is present in 48% to 65% of patients with OA and in more than 65% of patients over 80 years of age with OA requiring knee arthroplasty. Rosemann et al showed that osteoarthritic patients of both sexes have similar rates of hypertension (53%), high cholesterol (36%), heart failure (19%), diabetes mellitus (17%), and CAD (13%). Women with OA were found to have a lower quality of life and lower mood (P<0.01), a higher degree of disability (P<0.01), and to feel more pain (P<0.01).

In the large-scale AMICA study (Atrial Fibrillation Management in Congestive Heart Failure With Ablation) in Italy, which involved 3080 physicians and 29132 patients with OA, hypertension was found in 53% of study participants, type 2 diabetes in 15%, and history of myocardial infarction or angina in 6%. The degree of hypertension correlated with pain intensity, joint dysfunction, and worsening quality of life. Danish researchers found CVD in 54% patients with hip OA aged between 50 and 85 years. In Russia, a 1-year study of the rates of concomitant diseases associated with knee OA in an outpatient clinic also revealed twice higher rates of CAD, AH, and obesity, compared with patients without OA from the same clinic.

The increase in life expectancy has resulted in an aging population. Therefore, the combination of various chronic diseases with diseases of the musculoskeletal system, especially with OA, will be observed more and more frequently, and will affect not only health care systems, but also the quality of life. The relation between OA and comorbid disorders may be explained, to some extent, by common etiologic and pathogenetic mechanisms, or may be related to the biological processes of aging, which become more prevalent with age (such as cartilage degeneration, insulin resistance, weight gain, dyslipidemia, etc), and lead not only to the development, but possibly also to the maintenance of comorbidities.

OA and CVD are both considered to be age-related diseases. With aging, various human tissues accumulate advanced glycation end-products (AGEs), which play an important role in the pathogenesis of both atherosclerosis and OA. The formation of AGEs on the basement membrane of vascular walls leads to wall thickening, a narrowing of the lumen of capillaries, and reduced vascular wall elasticity, which can accelerate the development of the atherosclerotic process. AGEs also accumulate in human cartilage tissue, where they bind with the development of the atherosclerotic process. AGEs also accumulate in human cartilage tissue, where they bind with the development of the atherosclerotic process. AGEs also accumulate in human cartilage tissue, where they bind with the development of the atherosclerotic process.

Metabolic disturbances and nonspecific inflammation also play an important role in the pathogenesis of atherosclerosis and OA. Traditionally, OA has been considered to be a degenera-
tive disease of the joints, but accumulating evidence suggests that non-specific inflammation is also important in its pathogenesis.\textsuperscript{19,20} In OA, there are no classical macroscopic signs of inflammation and no severe infiltration by inflammatory cells in joint tissues. However, elevated levels of pro-inflammatory cytokines, interleukins (IL)-1, and tumor necrosis factor α (TNF-α) are observed in the synovial fluid of osteoarthritic patients. IL-1 stimulates the chondrocytes, thereby increasing the production of matrix metalloproteinases (MMPs)—proteolytic enzymes that degrade collagen and cartilage proteoglycans. Increased levels of MMP-3 were found in the synovial fluid and blood of patients with OA of the knee and hip joints. Moreover, serum levels of MMP-3 and MMP-9 were significantly higher in patients with hip OA compared with those with less severe OA.\textsuperscript{21} Therefore, MMP-3 and MMP-9 levels can serve as diagnostic markers of rapidly progressive OA. In addition, the chondrocytes of osteoarthritic individuals overexpress COX-2; this induces the synthesis of pro-inflammatory prostaglandins and the inducible form of nitric oxide synthase (iNOS), an enzyme that regulates the formation of nitric oxide and exerts a toxic action on the cartilage.

Epidemiological and immunopathological data suggest that inflammation is the major manifestation of atherosclerosis and is associated with dyslipidemia and chronic immune dysregulation.\textsuperscript{22,23} Pro-inflammatory cytokines and cell adhesion molecules expressed by vascular and blood cells play an important role in the pathophysiology of atherosclerosis. Prospective epidemiological studies have shown an association between the clinical manifestations of atherothrombotic disease and systemic markers of inflammation, including white blood cell count and various hemostatic proteins that reflect acute inflammation, such as fibrinogen, plasminogen activator inhibitor (PAI), and von Willebrand factor.\textsuperscript{20,24} C-reactive protein is directly involved in the pathogenesis of atherothrombosis and stimulates the production of tissue factor by the macrophages.

Tissue factor is the main inducer of coagulation in vivo and its local concentration in the arterial wall is associated with the development of events resulting in coronary thrombosis.\textsuperscript{25} In patients with a high risk of vascular complications, elevated levels of other markers of inflammation, such as IL-6, intracellular adhesion molecule-1 (ICAM-1), macrophage inhibitory cytokine-1 (MIC-1), and soluble CD40 ligand are also observed. Experimental studies have shown that the vascular endothelium and the smooth muscle cells of the arteries produce IL-6. At the same time, the IL-6 gene is expressed in areas of atherosclerotic lesions in man; therefore, IL-6 may also have procoagulant properties.\textsuperscript{25,26} Metalloproteinases take part in the remodeling of blood vessels and increase the rigidity of the arteries with age.\textsuperscript{27} Matrix metalloproteinase-3 (MMP-3) has been associated with lipid structures in atherosclerotic plaques and MMP-3 genotype may be an important determinant of age-related vascular remodeling and arterial stiffness.\textsuperscript{27} MMP-9 is involved in the rupture of the fibrous capsule of atherosclerotic plaques, and elevated levels of inhibitor of plasminogen activator-1 (PAI-1) are implicated in the process of thrombogenesis.\textsuperscript{28}

Another aspect of the association of vascular disease with OA relates to changes in the blood vessels of subchondral bone. The occurrence of OA and its subsequent progression are thought to be a consequence of atheromatous disease in these vessels.\textsuperscript{29,30} Bone is a highly vascularized tissue, and its vasculature is involved in all aspects of the growth, recovery, and metabolism of bone tissue. It is possible that in the context of vascular disease, episodic circulatory disorders take place in the subchondral bone, resulting in the development of OA. Subchondral bone ischemia, on the one hand, may lead to impaired nutrition and gas exchange in the articular cartilage, and thus trigger degenerative changes; on the other hand, it may promote osteocyte apoptosis in the subchondral bone, thereby inducing osteoclastic resorption.\textsuperscript{31,32}

The association of OA with CVD is probably determined not only by common pathogenetic mechanisms, but also by other external factors. Thus, the limitation of physical activity in patients with OA is a significant aggravating factor for cardiovascular disease. By inducing a neuroendocrine response, chronic pain is often the cause of complications in CVD patients. Pincus and Sokka have found that reduction in life expectancy in older people is determined, to a great extent, by the severity of pain.\textsuperscript{33} They assessed the survival rates of 1525 patients, of which 24% (370 patients) had OA, 16% (246 patients) had CVD, and 7.1% (109 patients) had OA and CVD. The results showed that the relative risk of death among patients with OA and a pain intensity of more than 40 mm on the visual analog scale (VAS) was higher than in patients with a pain intensity of less than 40 mm, without any significant differences according to age or sex.

**Osteoarthritis and obesity**

Obesity is among the most urgent health care and social problems of contemporary society. It is a risk factor not only for OA, but also for many other diseases associated with metabolic disturbances. OA, in turn, through the dysfunction and limitation of physical activity leads to an increase in body mass index (BMI) that can result in the development of CVD and diabetes. The risk of developing these conditions increases progressively with increasing BMI. In overweight patients with a 40% excess in body mass, the risk of premature death is twice that of people of average weight. In Russia, a study of 298 patients with overt OA of the knee and hip joints showed a marked increase in the prevalence of CVD and diabetes with increasing BMI.\textsuperscript{34}

Many studies have demonstrated an association between obesity (BMI >30) and OA of the knee, for both symptomatic and radiographic OA.\textsuperscript{35,36} Moreover, the risk of OA of the knee increases progressively with increasing BMI. Prospective stud-
ies have revealed that excess body mass contributes to the progression of the radiographic manifestations of knee OA. In a prospective cohort study, Wang et al found that both central obesity and the amount of fat mass represent risk factors for arthroplasty of the knee and hip joints. Interestingly, not only is increased body weight associated with an increased risk of OA, but it was also shown that weight loss causes a decrease in the risk of OA. A 2-kg/m² decrease in BMI was shown to reduce the risk of OA development by more than 50% at 10 years.

There is also some evidence of an association between obesity and OA of the joints of the hand. A study in female twins has shown that obesity is an important risk factor for the development of OA of the knee and carpal metacarpal joints, with a significant 9% to 13% increase in the risk of OA per each additional kilogram of body weight. A recently published systematic review confirms the existence of a positive association between body weight and OA development in the hands.

There is some controversy in the data published on the relationship between obesity and OA of the hip. Some researchers identified a clear correlation between BMI and the risk of hip OA, while others did not find any correlation at all.

However, a majority of studies have demonstrated an association between OA and obesity. Excess weight increases the load on the skeleton and causes lesions in bone and muscle tissue. Pressure-sensitive mechanoreceptors capable of triggering a signaling cascade were found on the surface of chondrocytes. Activation of these mechanoreceptors can lead to the expression of cytokines, metalloproteinases, prostaglandins, and nitric oxide. Experimental data show that, under certain conditions, overload can trigger the inhibition of matrix synthesis and degradation of cartilage. Obesity can potentially induce cartilage damage through activation of the mechanoreceptors.

Available data not only suggest an effect of overweight on the development of OA in the knee joints, but also confirm the existence of other mechanisms related to obesity that can change the metabolism of cartilage and bone tissue and lead to the development of OA. Adipose tissue is an active metabolic and endocrine organ producing hormones and bioactive substances, such as adipokines (also known as adipocytokines), that have various biological effects and underlie the association of obesity with concomitant diseases. Thus, leptin and adiponectin can have an influence on cartilage, bone tissue, and vascular walls. Adipokines, including leptin, are involved in the local modulation of articular cartilage metabolism. Elevated levels of leptin were found in both the synovial fluid and subchondral bone of osteoarthritic patients. Mainard et al demonstrated the importance of leptin in the pathogenesis of OA by showing its impact on the synthesis of insulin-like growth factor (IGF-1) and transforming growth factor-β1 (TGF-β1). Leptin, IGF-1, and TGF-β1 can be found in the cartilage of osteoarthritic patients (osteophytes), but not in the cartilage of disease-free patients. Moreover, osteophytes are associated with increased TGFβ1 expression. TGFβ1 induces fibrotic changes in the synovial membrane, bone sclerosis, and the differentiation of stem cells from the periosteal layer, resulting in the formation of osteophytes. An experimental study showed that injections of leptin into the joints of healthy rats caused symptoms of OA. In addition, Miller et al showed that a decrease in serum leptin levels may be one of the mechanisms by which weight loss slows down the progression of OA.

**Treatment of OA**

The data presented above suggest that we can consider OA as a disease that is pathogenetically related to cardiovascular diseases, obesity, and other metabolic conditions. As a result, the examination of OA patients should not be limited to the assessment of their articular disorder, but rather should be comprehensive, with particular attention paid to the state of their cardiovascular system. This highlights the importance of having an integrated approach when choosing a treatment, which should ideally combine nonpharmacological and pharmacological therapy. Patients should be informed about their condition, its main symptoms, and what may cause its progression. Patient education is, therefore, required in order to teach patients to follow an exercise regimen at work and at home and to perform regular aerobic exercise. Physical exercise regimens should be individualized, taking into account the presence of comorbidities and their severity. Patients should clearly understand that overweight, especially of the visceral type, is a confounding factor for the disease and, therefore, the target is not only to prevent weight gain, but also to reduce it. In addition, information should be provided on the use of orthopedic devices that facilitate the reduction of the load applied to the joints.

The main goals of pharmacological therapy in OA are effective pain relief, suppression of inflammation in the joint, improvement in functional capacity, and prevention of disease progression. When treating the clinical manifestations of OA in patients with obesity and other metabolic diseases (AH, CAD, etc)—or who are at high risk of their development—doctors should thoroughly think through their choice of therapy. In the presence of comorbidities, the excessive and unreasonable prescribing of drugs without first considering the particularities of their interactions can lead to a sharp increase in the risk of adverse effects and a worsening of the disease.

NSAIDs are commonly used to relieve pain in osteoarthritic patients, in accordance with the European League Against Rheumatism (EULAR), Osteoarthritis Research International (OARSI), and American College of Rheumatology (ACR) treatment guidelines. However, despite their being the most com-
monly prescribed drugs for the treatment of OA, NSAIDs were shown to cause a significant proportion of side effects in pharmaco-epidemiological studies, especially due to their improper use in elderly patients with comorbidities. Both selective and nonselective NSAIDs have pronounced anti-inflammatory and analgesic effects, but in patients with OA and metabolic diseases (obesity, AH, CAD, etc), or at high risk of developing them, they may cause a number of side effects that can aggravate the course of cardiovascular conditions. An increased risk of cardiovascular accidents (myocardial infarction, stroke, and sudden cardiac death) can be considered to be a class-specific side effect for all NSAIDs.\(^5\) NSAIDs can cause the destabilization of AH and progression of heart failure and it was found that NSAID treatment in patients with a history of heart disease increases the likelihood of hospitalization due to heart failure by 10 times (odds ratio=10.5), compared with patients not taking NSAIDs (odds ratio=1.6).\(^5\) Finally, it should also be borne in mind that NSAIDs can reduce the efficacy of drugs used in the conventional therapy of CVD (β-blockers, diuretics, angiotensin-converting enzyme inhibitors, and, to a lesser extent, calcium channel blockers).

**Conclusion**

Current data suggest that OA is a disease that is pathogenetically related to cardiovascular diseases and other metabolic conditions. The problem of comorbidity in patients with OA has clear prognostic significance. Early recognition of the comorbid conditions associated with OA and their comprehensive treatment with well-evidenced therapies will substantially reduce cardiovascular risks and improve patient prognosis.

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**Keywords:** arterial hypertension; cardiovascular system; comorbidity; metabolic disorder; obesity; osteoarthritis; pathogenesis; treatment goal

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**ARTHROSE ET COMORBIDITÉS**

L’arthrose est la pathologie la plus courante du système musculosquelettique et la cause principale de handicap et d’incapacité fonctionnelle chez l’adulte. D’après un nombre significatif d’études, les patients arthrosiques ont un risque nettement plus important de développer des comorbidités que ceux qui n’ont pas d’arthrose. L’arthrose se retrouve le plus souvent associée aux maladies cardiovasculaires, dont l’hypertension artérielle, à l’obésité, au diabète et aux maladies pulmonaires. L’association de diverses maladies chroniques avec des pathologies du système musculosquelettique, en particulier l’arthrose, va devenir de plus en plus fréquente et cela aura des conséquences non seulement sur les systèmes de soins de santé, mais aussi sur la qualité de vie. Les liens entre l’arthrose et les troubles comorbides peuvent s’expliquer, en partie, par des mécanismes étiologiques et pathogénétiques communs, ou peuvent être liés aux processus biologiques du vieillissement, qui peuvent conduire non seulement au développement, mais peut-être aussi au maintien des comorbidités. Les données présentées dans cet article suggèrent que l’arthrose est liée pathogénétiquement aux maladies cardiovasculaires, à l’obésité et à d’autres troubles métaboliques. Ainsi, l’examen des patients arthrosiques ne devrait pas se limiter à l’évaluation de leur pathologie articulaire, mais devrait être plus complet, en faisant particulièrement attention à leur système cardiovasculaire. Ceci souligne l’importance de l’usage d’une approche globale lors du choix des traitements dans l’arthrose.
Osteoarthritis (OA) is a disease not only of the cartilage, but also of the whole joint. In osteoarthritis and chronic inflammatory arthritides, the intensity of the inflammatory response of the joint determines juxta-articular bone loss. Thus, in rheumatoid arthritis, the intense synovial and cartilage inflammation, pannus formation, and systemic bone loss induce increased subchondral bone turnover with subsequent juxta-articular bone loss. By contrast, the mild and patchy synovitis seen in osteoarthritis results in lower subchondral bone turnover and less subsequent bone loss than in rheumatoid arthritis–like conditions. Angiogenesis and sensory nerve growth also contribute to joint damage to different extents in these arthropathies. However, the main underlying pathogenic mechanisms may be common among these joint diseases. A better understanding of the biological events involved in inflammation-induced bone loss in these diseases could lead to the identification of novel therapeutic strategies for the prevention of bone loss and also potentially progression of joint damage.

Effect of systemic osteoporosis on subchondral bone structure and remodeling

Systemic osteoporosis (OP) alters the microstructural and biological properties of subchondral bone. Compared with normal and osteoarthritic femoral heads, the femoral heads of patients with OP show the least stiff and dense subchondral bone plates (OA femoral heads show values in between normal and OP femoral heads). Although osteoporotic bone has been found to contain less mineral, its organic and water contents have been found to be proportionally higher, suggesting no change in the relative amount of organic matrix.1 Studies in different animal models have reported that OP has a negative effect on subchondral bone integrity.6-10 In an experimental model of OP in rabbits, which was induced by glucocorticoid administration and ovariectomy, subchondral bone mineral density was significantly lower compared with controls.8 This experimental model also showed a decrease in subchondral plate thickness and only a negative tendency in bone area fraction and trabecular thickness values, while the microarchitecture index fractal dimension was increased. The decrease in subchondral plate thickness would indicate that this experimental model of OP exhibits a much more profound effect on subchondral cortical bone than subchondral trabecular bone. Increased remodeling in favor of subchondral bone resorption has also been reported in osteoporotic rabbit-related studies, as determined by reduced alkaline phosphatase expression and increased matrix metalloproteinase (MMP)-9 expression, also supported by a decrease in the osteoprotegerin (OPG)/receptor activator of nuclear factor-kB ligand (RANKL) ratio compared with healthy controls.8 In ovariectomized sheep, bone volume fraction was found to be reduced in subchondral bone compared with controls. Trabeculae were also significantly thinner in these animals, with reduced connectivity density, and significant alterations observed in the trabecular architecture under the tibial plateau following 12 months of estrogen deficiency.10 Lastly, in an ovariectomized mouse model, use of either estrogen supplementation or bisphosphonate treatment resulted in inhibition of tibial and patellar subchondral cortical thinning.11 Taken together, these studies demonstrate a relevant and negative effect of systemic OP on the structure and metabolism of subchondral bone.

Influence of osteoporosis in the remodeling of subchondral bone in osteoarthritis

It is increasingly acknowledged that articular cartilage homeostasis is dependent on the integrity of the underlying bone.8-10 Several studies have identified specific changes that occur to the architecture and turnover of subchondral bone in OA.16,17 The study of the influence of OP on subchondral bone remodeling could reveal relevant mechanisms involved in the development of OA. Thus, our group developed a rabbit model of surgically-induced OA preceded by OP, and demonstrated that microstructure impairment in subchondral bone associated with increased remodeling increases cartilage damage.8 Indeed, compared with control and OA knees, OPOA knees demonstrated diminished subchondral bone area/tissue area, trabecular thickness, and polar moment of inertia, as well as a pronounced decline in subchondral plate thickness. Compared with controls, the subchondral bone of OA, OP, and OPOA knees showed a decrease in alkaline phosphatase expression and OPG/RANKL ratio as well as an increase in the fractal dimension and MMP-9 expression. In addition, the severity of cartilage damage was increased in OPOA knees versus controls. Remarkably, good correlations were observed between structural and remodeling parameters in subchondral bone, and furthermore, between subchondral structural parameters and cartilage Mankin score.

In line with our results, a decrease in subchondral plate thickness was also reported in an ovariectomized murine model of intra-articular iodoacetate-induced knee OA,11 as well as in experimental models of OA evaluating the early disease stage.13,14,16-20 Thinning and porosity of the subchondral plate were only present in the medial compartment and were related to superjacent cartilage damage, while in the canine anterior cruciate ligament transection (ACLT) model, trabecular bone changes were mostly found in the lateral compartment and were related to mechanical unloading. Thickening of the subchondral plate has, however, been described in animal models of surgically-induced OA corresponding to late-stage disease.13,19,21 Remarkably, in some of these studies, the early decrease in subchondral plate thickness was followed by late plate thickening.13,15 Furthermore, in the rat ACLT and meniscectomy models of OA, increased mRNA levels of cathepsin K and tartrate-resistant acid phosphatase were found in subchondral bone at week 2 post-surgery, as well as invasion of cathepsin K+ osteoclasts into the articular cartilage from the subchondral region. These events thus confirm that bone resorption is an early event in the disease course of OA. Upregulation of the osteoanabolic mark-

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In human knee OA, cartilage damage is frequently associated with thickening of the subchondral plate and osteophyte formation. Aside from this hypertrophic OA, some authors consider that there is another variant, the atrophic form, which is characterized by a lack of osteophytes and loss of subchondral bone volume in OA patients with compromised hip and knee. This atrophic form probably shares several etiopathogenic mechanisms and phenotypic features with OA associated with OP (Table). Furthermore, the correlation observed in hypertrophic OA between serum levels of C-propeptide and type II collagenase has been found to be lost in atrophic OA, the latter showing reduced type II collagen synthesis. This could contribute to the absence of osteophyte formation as well as the increased subchondral bone turnover seen in rapidly progressive hip and knee OA. Of note, the presence of osteoporosis (OP) probably shares common development events with OA associated with OP (Table).

**Effects of systemic osteoporosis in osteoarthritis**

A complex and paradoxical relationship seems to exist between OA and OP, although there is increasing evidence to support a close biomolecular and mechanical association between subchondral bone and cartilage. Indeed, microarray profiles have identified a number of genes differentially expressed in osteoarthritic bone that are key players in the structure and function of both bone and cartilage. These include genes involved in the Wingless-type mouse mammary tumor virus/β-catenin (Wnt/β-catenin) and transforming growth factor-β/mothers against decapentaplegic (TGF-β/SMAD) signaling pathways and their targets. Furthermore, aggrecan production, as well as SOX9, type II collagen, and parathyroid hormone–related protein mRNA expression, were inhibited in sclerotic but not nonsclerotic osteoblasts, while expression of MMP-3, MMP-13, and osteoblast-specific factor 1 by human OA chondrocytes was augmented in a coculture system. Thus, sclerotic osteoarthritic subchondral osteoblasts may contribute to cartilage degradation and chondrocyte hypertrophy. In addition, in our animal model of OA preceded by OP, improvement in subchondral bone integrity was shown to reduce the progression of cartilage damage, suggesting a direct relationship between these two conditions. On the other hand, several cross-sectional studies have demonstrated an inverse relationship between OP and OA, although others have produced opposite results. Confounding variables such as race, obesity, and physical activity could explain the mutually exclusive relationship between OA and OP, whereby overweight individuals and/or those who undertake excessive physical activity could have a higher risk of developing OA and having a higher bone mass.

<table>
<thead>
<tr>
<th>Disease type</th>
<th>Subchondral bone remodeling</th>
<th>Systemic osteoporosis</th>
<th>Cartilage inflammation</th>
<th>Role of osteoporosis in disease progression (cartilage degradation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophic OA*</td>
<td>++ (toward resorption)</td>
<td>++</td>
<td>++</td>
<td>++ (predominantly joint space narrowing)</td>
</tr>
<tr>
<td>Hypertrophic OA</td>
<td>++ (toward formation)</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>+++ ?</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
</tbody>
</table>

*Atrophic OA probably shares common development events with OA associated with osteoporosis. +/- presence or absence; + mild; ++ moderate; +++ severe.

Recently, we proposed that high as well as low bone mass conditions can result in OA induction and/or progression. Thus, both bone mass phenotypes may be considered risk factors for OA initiation. The presence of other risk factors such as skeletal shape abnormalities, joint overload, or obesity may have a synergistic effect regarding OA initiation. In addition, inflammatory mediators released by the articular cartilage in OA may lead to subchondral bone loss through increased

**Table.** Etiopathogenic mechanisms and phenotypic features of atrophic osteoarthritis (OA), hypertrophic OA, and rheumatoid arthritis, and the involvement of osteoporosis.
bone remodeling. Accordingly, treatment goals for OA must consider improvement of subchondral bone integrity. This therapeutic approach should be individualized according to the patient’s bone mineral density status and OA phenotype, and the use of drugs should also subsequently be individualized for each patient. Recent findings suggest that the same drugs could be useful for treating both processes simultaneously, at least in a subgroup of patients with OA and concomitant OP.30

**Effect of chronic synovitis on subchondral bone remodeling**

Juxta-articular bone loss is related to the intensity of the inflammatory response in the affected joint.36,37 This fact is observed not only in rheumatoid arthritis, but also in other arthritides associated with a high degree of inflammation.38,39 Juvenile idiopathic arthritis, seronegative spondyloarthropathies, systemic lupus erythematosus, as well as septic arthritis, are all rheumatic diseases in which intense inflammation is associated with skeletal pathology. Although some of the mechanisms of skeletal remodeling are shared among these diseases, each disease has a unique impact on articular bone or the axial or appendicular skeleton.39

Various hormones, cytokines, and chemokines produced by the inflamed synovial membrane have been reported to be involved in juxta-articular osteoporosis in these diseases.36 The inflammatory mediators modulate the expression of the crucial factor RANKL, in whose presence macrophages differentiate into bone-resorbing osteoclasts in zones of contact between the inflamed synovium and subchondral bone, as described in rheumatoid arthritis.40 In addition to membrane-bound RANKL in osteoblasts, RANKL secreted by synovial cells actively promotes bone destruction in chronic inflammatory arthritis.37 Hence, high local RANKL concentrations lead to increased osteoclastogenesis at the bone-pannus interface.

We have recently described that RANKL expressed by chondrocytes also contributes significantly to the pathogenesis of the juxta-articular bone loss associated with chronic arthritis in a rabbit model that develops a more intense and destructive version of the well-established antigen-induced arthritis (AIA).41 This experimental arthritis was found to be accompanied by severe juxta-articular bone loss, as estimated by x-ray and bone mineral density measurement. The increase in RANKL expression in the cartilage of AIA rabbits was linked to the particular presence of extracellular RANKL in the calcified cartilage. Previous results from our group have also shown that RANKL is localized in the extracellular matrix of human OA cartilage and could reach the subchondral bone through the calcified cartilage.42 These results indicate that chondrocyte-synthesized RANKL acts on subchondral bone cells, stimulating juxta-articular bone loss. Other studies have demonstrated that soluble RANKL produced by hypertrophic chondrocytes is a biologically active molecule during bone growth,43 acting in a paracrine manner on the subchondral bone plate. We have also shown that RANKL synthesized by prostaglandin E2–stimulated mature articular chondrocytes is also biologically active and is responsible for the mononuclear cell differentiation into osteoclast in the absence of exogenous RANKL.41

By contrast, in OA, mild synovial hyperplasia is predominantly present, with proliferation and activation of lining cells associated with fibrosis-related changes.44,45 Synovial inflammatory infiltrates are composed of mononuclear cells that appear in far less abundance than in the synovium in rheumatoid arthritis, and they are distributed in a patchy pattern, mostly confined to areas adjacent to sites of damaged cartilage, thereby increasing OA severity throughout the disease course.46,47 The inflammatory synovial changes are associated with increased production of proinflammatory cytokines and mediators of OA joint damage.48 The Krenn synovitis score was found to be well correlated with subchondral bone structural parameters in an experimental model of OA preceded by OP.46 Furthermore, rabbits with surgery-induced knee OA showed a lower synovial inflammatory response and less subchondral bone loss than rabbits with AIA.49 Remarkably, RANKL expression in OA cartilage—particularly in calcified cartilage—was less than in AIA cartilage, suggesting that the relevant involvement of this osteoclastogenic molecule in subchondral bone loss in OA is smaller in degree than in chronic inflammatory arthritis.47

In addition, inflammation drives synovial angiogenesis through macrophage activation, which in turn perpetuates inflammation and synovial hyperplasia, inducing pannus formation to variable extents. This is a well-recognized pathogenic mechanism in the rheumatoid arthritis joint. Novel studies, however, have identified the presence of increased angiogenesis in the synovium, osteophytes, menisci, and osteochondral junction in OA patients.50 Channels extending from subchondral bone into noncalcified articular cartilage provide the anatomical basis for angiogenesis and sensory nerve growth through the osteochondral junction. Thus, to different extents, angiogenesis also contributes to structural damage in chronic joint diseases.50

In summary, the intensity of the inflammatory response of the joint determines the juxta-articular bone loss in OA and chronic inflammatory arthritides. In articular conditions such as rheumatoid arthritis, the intense synovial and cartilage inflammation, pannus formation, and systemic bone loss will lead to high production of key biological mediators such as RANKL, which are involved in increased subchondral bone turnover with subsequent juxta-articular bone loss. By contrast, during the OA disease process, mild and patchy synovitis will occur with less RANKL expression in cartilage, resulting in lower subchondral bone turnover and subsequent bone loss than in rheumatoid arthritis—like conditions. In addition,
angiogenesis and sensory nerve growth also contribute to joint damage to varying extents in these arthropathies. However, the main underlying pathogenic mechanisms may be common among these joint diseases. Further elucidation of the biological events involved in inflammation-induced bone loss will potentially lead to the identification of novel therapeutic strategies for the prevention of bone loss, and potentially joint damage progression, in these diseases.

**Keywords:** inflammatory arthritis; osteoarthritis; subchondral bone

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**Physiopathologie de l’arthrose : ressemblances et différences avec d’autres pathologies rhumatoïdiennes ; le rôle de l’os sous-chondral**

L’arthrose est non seulement une pathologie du cartilage mais aussi de toute l’articulation. Dans l’arthrose et les arthrites inflammatoires chroniques, l’intensité de la réponse inflammatoire de l’articulation détermine la perte osseuse juxta-articulaire. Ainsi, dans la polyarthrite rhumatoïde, l’inflammation intense du cartilage et de la synovie, la formation de pannus et la perte osseuse généralisée provoquent une augmentation du renouvellement osseux sous-chondral entraînant une perte osseuse juxta-articulaire. À l’inverse, la synovite modérée et clairsemée de type arthrosique conduit à un renouvellement osseux sous-chondral plus faible et à une perte osseuse ultérieure moins importante que dans la polyarthrite rhumatoïde. L’angiogenèse et la croissance des nerfs sensoriels contribuent également à causer des lésions articulaires de sévérité différente dans ces arthropathies. Toutefois, les principaux mécanismes pathogènes sous-jacents sont probablement communs à ces maladies articulaires. De nouvelles stratégies thérapeutiques pour prévenir la perte osseuse et, éventuellement, l’évolution des lésions articulaires pourraient être élaborées si les phénomènes impliqués dans la perte osseuse provoquée par l’inflammation au cours de ces maladies étaient mieux compris.
Osteoarthritis is a highly prevalent joint disorder primarily affecting elderly people worldwide. The importance of imaging for assessment of all the structures of the joint such as cartilage, meniscus, subarticular bone marrow, and synovium for diagnosis, prognostication, and follow-up has been well recognized over the past decade. Conventional radiography is still the most commonly used imaging technique for evaluation of a patient with a known or suspected diagnosis of osteoarthritis. However, recent MRI-based knee osteoarthritis studies have begun to reveal the limitations of radiography. The ability of MRI to image the knee as a whole organ and to directly and three-dimensionally assess cartilage morphology and composition plays a crucial role in understanding the natural history of the disease and in guiding future therapies due to its ability to image the knee as a whole organ and to directly and three-dimensionally assess cartilage morphology and composition.

Role of imaging in osteoarthritis: diagnosis, prognosis, and follow-up

by A. Guermazi, F. W. Roemer, and H. K. Genant, USA and Germany

Osteoarthritis (OA) is a highly prevalent joint disorder and is becoming increasingly common, posing major health and economic challenges for aging industrialized societies. Despite various surgical and symptom-oriented approaches, there is still no definitive disease-modifying therapy, other than total joint replacement, for this complex and heterogeneous disease.

Most research studies of knee OA involve acquisition of conventional radiographs and magnetic resonance images, including the Osteoarthritis Initiative (OAI, http://www.oai.ucsf.edu/datarelease/), one of the largest epidemiological OA studies. The OAI is an ongoing 4-year observational study of approximately 4800 participants, sponsored by the National Institutes of Health, and targeted at identifying the most reliable and sensitive biomarkers for evaluating the development and progression of symptomatic knee OA. Data from baseline through the 48-month follow-up visit for the entire cohort were made publicly available in 2011. This article aims to describe the current role of radiography and magnetic resonance im-
aging (MRI) in OA imaging, and also to give some insight into the use of other modalities: ultrasound, nuclear medicine, and computed tomography (CT). Current research tends to focus on the knee due to the high prevalence of knee OA and the relative ease of use of MRI compared with other central appendicular joints. This nonsystematic review article will focus primarily on the assessment of OA in the tibiofemoral joint of the knee.

Conventional radiography
Radiography is the simplest and least expensive imaging technique. It can detect OA-associated bony features including marginal osteophytes, subchondral sclerosis, and subchondral cysts. Radiography can also determine joint space width (JSW), an indirect surrogate of cartilage thickness and meniscal integrity, but precise measurement of each of these articular structures is not possible by x-ray. Despite this, slowing of radiographically detected joint space narrowing (JSN) is the only structural end point currently recommended by the regulatory bodies in the United States (US Food and Drug Administration [FDA]) and in Europe (European Medicines Agency [EMA]) to prove the efficacy of disease-modifying OA drugs in phase-3 clinical trials. OA is defined radiographically by the presence of osteophytes. Progression of JSN is the most commonly used criterion for the assessment of OA progression and the complete loss of JSW characterized by bone-on-bone contact is one of the indicators for joint replacement.

The severity of OA can be estimated using semiquantitative scoring systems. Published atlases provide images that represent specific grades. The most widely used system, the Kellgren and Lawrence (K&L) classification, has limitations, especially as K&L grade 3 includes all degrees of JSN, regardless of the actual extent. In contrast, the Osteoarthritis Research Society International (OARSI) atlas classification grades tibiofemoral JSW and osteophytes separately for each compartment of the knee. Compartmental scoring appears to be more sensitive to longitudinal radiographic changes than K&L grading.

Methods of JSW measurement can be manual or semiautomated using computer software. However, previously held beliefs that JSN and its changes are the only visible evidence of cartilage damage have been shown to be incorrect. Recent studies have demonstrated that alterations in the meniscus, such as meniscal extrusion or subluxation, also contribute to JSN. The lack of sensitivity and specificity of radiography for the detection of the pathologic features associated with OA, and the poor sensitivity to change at follow-up imaging, are inherent limitations of radiography.

Interestingly, an older method—digital tomosynthesis—has lately experienced a revival. Tomosynthesis generates an arbitrary number of section images from a single pass of the x-ray tube. Using 3T MRI as a reference, Hayashi et al found that tomosynthesis depicted more osteophytes and subchondral cysts than radiography. The clinical availability of these systems is currently limited, but the potential of this technique for OA research may be worth exploring.
Magnetic resonance imaging
MRI offers a number of advantages for OA imaging. First, MRI has a tomographic viewing perspective and thus provides cross-sectional images of the anatomy free of the projectional limitations of radiography. Second, MRI is uniquely able to directly depict all the components of the joint and their pathologies, including the articular cartilage, menisci, intra-articular ligaments, synovium, effusion, bone attrition, bone marrow lesions (BMLs), subchondral cysts, and intra- and periarticular cystic lesions (Figure 2). The joint can be evaluated as a whole organ, providing a much more detailed picture of the changes associated with OA than is possible with other techniques. Third, MRI can detect the pathology of preradiographic OA and possible complications of the disease at a much earlier stage than radiography.

Technical considerations
Several MRI systems are commercially available but 1.5T systems are the most widely used in clinical and research settings. Examination times vary depending on the purpose of the exam, but usually last between 20 and 40 minutes, including patient positioning. High-field 3T MRI was introduced for clinical application several years ago. A higher signal-to-noise ratio is a definitive advantage, but disadvantages include increased susceptibility artifacts, high costs, and the limited commercial availability of coils. Most OA studies that include MRI use 1.5T MRI systems because of their wide availability and reliable image quality. The OAI is one of the few large studies to have used a 3T system (Figure 3).

So far, 7T MRI in humans has only been applied in research. In the future, 7T systems may be able to produce higher-resolution images with a shorter scan time than 3T systems. So far, however, the available 7T protocols have not been any better than 3T for knee cartilage evaluation.

The role of contrast-enhanced MRI (CE-MRI) in the clinical and research environment remains to be fully established. Visualization of synovitis in OA is superior on contrast-enhanced scans using the intravenous paramagnetic agent gadolinium with histological correlation, and recent studies have shown that CE-MRI-detected synovitis is associated with knee pain (Figure 4).

Since different tissues are involved in OA and both morphologic and quantitative analyses are needed, a variety of different sequences have been developed for “whole-organ” assessment of OA. Selecting the appropriate MR pulse sequences to study specific features of OA is essential for success. In general, fluid-sensitive fat-suppressed sequences (eg, T2-weighted, proton-density-weighted, or intermediate-weighted fast spin-echo sequences) are useful for evaluation of cartilage, bone marrow, ligaments, menisci, and tendons. It is particularly important to use these sequences to assess focal cartilage defects and BMLs. Gradient-recalled echo (GRE)-type sequences (eg, 3D-spoiled gradient echo at steady state [SPGR], double-echo steady state [DESS], and fast low-angle shot [FLASH]) are not suitable for marrow or focal defect assessment. They are prone to susceptibility artifacts, which...
hinder accurate interpretation of images.\textsuperscript{14} GRE-type sequences also usually require long imaging times, and motion artifacts can degrade image quality.\textsuperscript{15} A recent study demonstrated that focal cartilage lesions were more conspicuous and larger on the intermediate-weighted fast spin-echo sequence with fat suppression compared with the DESS sequence.\textsuperscript{16} It was also shown that GRE-type sequences have limited sensitivity to BMLs compared with fast spin-echo sequences (Figure 5).\textsuperscript{17} For synovitis, CE-MRI is preferable to non–CE-MRI, but if only non–CE-MRI is available, gradient-echo type sequences should again be avoided because they are prone to chemical shift artifacts, making accurate assessment difficult.\textsuperscript{18}

On the other hand, GRE-type sequences do provide high spatial resolution and excellent contrast of cartilage to subchondral bone, and are well suited for quantitative measurement of volume and thickness.\textsuperscript{15} MRI is a powerful tool for OA research, but it is also complex and how it is used is largely determined by the goal of the research. Clinicians planning clinical OA research using MRI-derived data should seek expert advice from trained and experienced musculoskeletal radiologists on which pulse sequences are best suited to their purpose.

\textbf{Semiquantitative MRI whole-organ scoring}

Semiquantitative whole-organ scoring has been applied to a multitude of OA studies.\textsuperscript{7,19} Analyses based on semiquantitative scoring have added greatly to our understanding of the pathophysiology and natural history of OA as well as to the clinical implications of structural changes. A short list of semiquantitative scoring systems includes the Whole-ORGan Magnetic resonance imaging Score (WORMS),\textsuperscript{7} the Knee Osteoarthritis Scoring System (KOSS),\textsuperscript{20} the Boston Leeds Osteoarthritis Knee Score (BLOKS),\textsuperscript{21} and the MRI OsteoArthritis Knee Score (MOAKS).\textsuperscript{22} MOAKS is a recent effort to combine the strengths of existing systems, but little information on its use has been published to date. In addition to these scoring systems based on non-enhanced MRI, semiquantitative scoring systems for synovitis using contrast-enhanced MRI have been proposed.\textsuperscript{12,23,24,25} In particular, the system proposed by Guermazi et al enables comprehensive assessment of synovitis in the whole knee joint,\textsuperscript{12} rather than being restricted to the peripatellar regions.\textsuperscript{23} These contrast-enhanced MRI–based scoring systems will enable longitudinal assessment of synovitis in future clinical trials.\textsuperscript{12}

Recently, MRI-based semiquantitative scoring systems for hand OA (Oslo Hand OA MRI score [OHOA-MRI]) and hip OA (Hip OA MRI Scoring system [HOAMS]) have been proposed.\textsuperscript{24,25} However, further validation, evaluation of responsiveness, and iterative refinement of these new systems are needed to assess their utility in clinical trials and epidemiological studies. To the authors’ knowledge, no semiquantitative scoring systems enabling evaluation of other joints, such as the shoulder, elbow, and ankle, as a “whole joint” have been published. A limited number of small studies have been published recently involving cartilage repair techniques or novel imaging methodologies for these joints.\textsuperscript{26}

\textbf{Compositional imaging of cartilage}

Compositional MRI can assess the biochemical properties of different joint tissues and is thus very sensitive to early morphologic changes. The vast majority of studies applying compositional MRI have focused on cartilage, although the technique can also be used to assess other tissues such as the meniscus or ligaments.\textsuperscript{27} T2 mapping has been used to describe the molecular composition of hyaline cartilage in the knee on the basis of collagen structure and hydration.
In healthy cartilage, T2 values increase from deep to superficial cartilage layers.\textsuperscript{28} It has been shown that T2 values are related to age and activity levels and that they are associated with OA severity.\textsuperscript{29,30} T2* relaxation measures have also been tested for their ability to depict the collagen matrix. T2* mapping was shown to be a reproducible process that can differentiate between OA and non-OA subjects.\textsuperscript{31}

T1rho is also sensitive to the interactions of water with macromolecules. It has been shown to correlate with the proteoglycan concentration in cartilage,\textsuperscript{32} and is also sensitive to collagen.\textsuperscript{33} Although T1rho has been shown to have a larger dynamic range than T2,\textsuperscript{34} it is more complex to implement, and is limited by radiofrequency power deposition. It has been reported that T1rho and T2 values show different spatial distributions and may provide complementary information on cartilage degeneration.\textsuperscript{35}

Sodium MRI and the delayed gadolinium-enhanced MRI of cartilage technique (dGEMRIC) are designed to measure fixed charge densities in cartilage and, by implication, its proteoglycan content \textsuperscript{36} These techniques are based on the premise that mobile ions will distribute themselves in cartilage in relation to the concentration of the charged proteoglycan molecules; in MRI, the mobile ions are the naturally abundant sodium, or the negatively charged MRI contrast agent Gd(DTPA)\textsuperscript{2−} (Magnevist, Berlex, NJ, USA).

In the dGEMRIC technique, Gd(DTPA)\textsuperscript{2−} is injected intravenously, and images are acquired typically around 90 minutes after injection. The negative charge on the Gd(DTPA)\textsuperscript{2−} molecule causes it to disperse into the cartilage in inverse relation to the negatively charged glycosaminoglycan molecular concentration.\textsuperscript{37} A recent interventional study evaluating the effect of weight loss on articular cartilage showed an improvement in cartilage quality reflected by an increase in the dGEMRIC index over 12 months in the medial but not in the lateral tibiofemoral compartment. This finding supports the notion that body weight affects disease progression and emphasizes the role of weight loss in clinical and structural improvement.\textsuperscript{38}

Novel compositional techniques have been reported. Raya et al studied the feasibility of in vivo diffusion tensor imaging at 7T MRI and demonstrated better discrimination of OA versus non-OA knees than with T2 mapping.\textsuperscript{39} Although this technique shows promise, it will have to be more practical and widely available for use with standard MRI systems before it can be applied in broader clinical research settings.

Figure 6. Biochemical magnetic resonance imaging.  
(A) Sagittal intermediate-weighted fat-saturated image depicts a horizontal-oblique tear of the posterior horn of the medial meniscus (arrow).  
(B) Corresponding baseline color-coded T1-weighted image showing normal delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) map of femoro-tibial cartilage.  
(C) At 24 months there is a marked decrease in the dGEMRIC index in the medial femoral cartilage (coded in red - arrowheads). An incidental partial meniscal maceration is also seen (arrow).
anatomical subregions and radiography.42

Ultrasound
Ultrasound is a technique that enables multiplanar and real-time imaging at a relatively low cost, without radiation exposure. It has the ability to image soft tissue and to detect synovial pathology without the need for contrast administration. Limitations of ultrasound are primarily that it is an operator-dependent technique and that the physical properties of sound hinder its application to deeper articular structures and the subchondral bone. The ability to detect synovial pathology is perhaps the major advantage of ultrasound over radiography. Ultrasound-detected grey-scale synovitis has been validated against arthroscopy, MRI, and histology in large-joint OA, and ultrasound has been demonstrated to be more sensitive than clinical examination in detecting synovial hypertrophy and joint effusion.43 Additionally, color-coded Doppler signal has been validated as an indirect measure of histological synovial vascularity in large-joint OA.44 Tissues other than synovium have also been studied using ultrasound. Saarakkala et al compared knee ultrasonography to arthroscopic grading for detecting degenerative changes in articular cartilage.45,46 The authors concluded that positive findings on ultrasound are strong indicators of degenerative changes in cartilage, but also stated that negative findings do not rule out degenerative cartilage alterations. A study by Kawaguchi et al used ultrasound to look at medial radial displacement of the meniscus in the supine and weight-bearing positions and showed that the medial meniscus was significantly displaced radially by weight bearing in control knees and in knees with K&L grades 1-3.46 Its use with dynamic and weight-bearing conditions is one of the inherent strengths of ultrasound and warrants further exploration.

Computed tomography
CT is a valuable tool for the characterization of OA, particularly when imaging of osseous changes or detailed presurgical planning is required. Helical multidetector (MD) CT systems enable acquisition of isotropic voxels and multiplanar reconstructions in any given plane with quality equal to the original plane. Cortical bone and soft tissue calcifications are better depicted than on MRI. CT has an established clinical role in assessing facet joint OA of the spine.47 Drawbacks are its low soft-tissue contrast and the relatively high dose of radiation it delivers. CT arthrography is an alternative method for indirect visualization of cartilage and other intrinsic joint structures, especially in the knee joint. CT arthrography may be relevant especially where access to MRI facilities is limited or when MRI is contraindicated. Spiral CT arthrography of the knee and shoulder enables excellent imaging of the articular surface. Penetration of contrast medium into the deeper layers of the cartilage surface indicates an articular-side defect of the chondral surface. The high spatial resolution and the high attenuation difference between the cartilage and the contrast medium within the joint make focal morphologic changes conspicuous. Limitations of the technique are its insensitivity to changes of the deep layers of cartilage without surface alterations and its invasive nature.

Nuclear medicine
Scintigraphy uses radiopharmaceuticals to visualize skeletal metabolism, to contribute to the localization of disease, and to assess the severity of pathologic changes in OA.50 TC-hydroxymethane diphosphonate scintigraphy shows increased activity during the bone phase in the subchondral region in nodal hand OA.45 This finding can be observed before the typical radiographic changes and reflects the osteoblastic activity of early cartilage loss. A study comparing MRI with scintigraphy in patients with chronic knee pain demonstrated good agreement between MRI-detected subchondral BMLs and radionuclide uptake, but generally poor agreement between increased bone uptake and cartilage defects or osteophytes.50 A prospective study showed that a normal bone scan at baseline was highly predictive of a lack of progression of knee OA over a 5-year period.51 Two other recent studies showed that scintigraphy may predict JSN, but no better than baseline radiographic or pain status.52,53

Positron emission tomography (PET) demonstrates metabolic changes in target tissues and can detect foci of inflammation, infection, and tumors. PET utilizes 2-[18F]-fluoro-2-deoxy-D-glucose (FDG) and reflects glucose metabolism. A recent pilot study in knees with medial OA showed increased uptake in periarticular regions, the intercondylar notch, and also in areas of subchondral bone marrow corresponding to MRI-detected BMLs.44 A recent animal study showed increased uptake of FDG after experimentally induced knee OA in rats, suggesting that PET could be useful for early detection of OA changes.54 However, whether FDG-PET will have a role in the assessment of OA in a clinical and research setting remains to be seen. Limitations of PET include its limited availability, high radiation exposure, and costs.

Conclusion
Conventional radiography is still the first and most widely used imaging technique for evaluation of a patient with a known or suspected diagnosis of OA. In research and clinical trials it is the only EMA- and FDA-recommended imaging modality for defining the inclusion criteria and efficacy end points of a clinical trial. However, radiography has its limitations and well-defined MRI-based diagnostic criteria of OA are needed. MRI plays a crucial role in understanding the natural history of the disease and in guiding future therapies due to its ability to image the knee as a whole organ and to directly and three-dimensionally assess cartilage morphology and composition. Ultrasound and contrast-enhanced MRI play important subsidiary roles in the diagnosis and follow-up of treatment of OA-related synovitis.
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Keywords: magnetic resonance imaging, osteoarthritis, radiography, ultrasound

**RÔLE DE L’IMAGERIE DANS L’ARTHROSE : DIAGNOSTIC, PRONOSTIC, ET SUIVI**

Osteoarthritis treatments: where do we stand at the moment?

by C. Roubille, J. Martel-Pelletier, and J. P. Pelletier, Canada

Osteoarthritis is the most common form of arthritis and results in pain and reduced quality of life. Although a structure-modifying treatment remains the greatest unmet need in osteoarthritis, several symptomatic treatments are available. This article will review the nonpharmacological approaches and pharmacological treatments currently available for osteoarthritis management, as well as the surgical treatments available for the condition. At present, a multimodal approach combining nonpharmacological and pharmacological treatments is still the best option for the management of osteoarthritis, as recommended in the guidelines of Osteoarthritis Research Society International and the American College of Rheumatology.

Nonpharmacological management mainly relies on patient education, exercise, prevention of injuries, weight loss in overweight patients, and use of orthotic devices. Pharmacological symptomatic treatments include a number of analgesic options such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, duloxetine, topical NSAIDs, capsaicin, lidocaine patches, intra-articular corticosteroids and hyaluronic acid injections, and slow-acting drugs including glucosamine and chondroitin sulfate, diacerein, and avocado soybean unsaponifiables. When the combination of nonpharmacological and pharmacological approaches becomes unsuccessful at managing symptoms, surgical treatment may be considered.

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Patient education
Patient education should form the cornerstone of nonpharmacological management for osteoarthritis,2,3 and patients should be involved in the management of their condition as much as possible.4 Indeed, as with other chronic diseases, patients should know about their condition’s evolution over time as well as its management and any associated investigations, and this can be achieved through use of books, regular telephone calls, and education groups. It has been suggested that education contributes to pain reduction and optimization of health care resource usage.6

Exercise programs
Physical activity involving aerobic and/or resistance land-based exercises and/or aquatic exercises, including local muscle strengthening and general fitness, is recommended for osteoarthritis patients.1 Strengthening exercises, especially for the quadriceps femoris muscle, may improve muscular balance, decrease impact loads, and support function, and they have also been reported to reduce pain and disability in hip6 and knee osteoarthritis.6 Water-based exercises have been shown to have short-term effects on pain relief for patients with hip and/or knee osteoarthritis.7 In addition, contrary to popular belief, running—even long distances—as part of normal nonprofessional conditioning does not accelerate the development of osteoarthritis of the knee.8 However, the risk of osteoarthritis development may be different for middle-intensity levels of running compared with high or competitive levels: moderate regular running may be safe, whereas professional runners may have an increased risk for osteoarthritis.9,10

Prevention of injuries
Prevention of injuries is necessary in contact sports such as soccer.11 Increased joint traumatisms such as anterior cruciate ligament lesions or meniscal lesions increase the risk of developing osteoarthritis. Effective treatment such as postoperative rehabilitation should decrease this risk.

Weight loss
Does weight loss reduce osteoarthritis symptoms and prevent overall progression of structural damage? This is a most important and relevant question in the management of osteoarthritis. In obese patients, weight loss and maintenance of weight at a lower level seems to reduce osteoarthritis-related pain.12 Weight loss in obese people was reported to improve the content of the macromolecule proteoglycan in the cartilage, as well as the cartilage thickness in the medial, but not lateral, compartment of the knee.13 Interestingly, obesity increases the risk of progressive osteoarthritis in neutrally aligned knees or those in varus alignment, but not in patients with valgus alignment.14 Thus, overload alone across the joints does not seem to be sufficient to induce the development of osteoarthritis. As obese individuals also have a higher incidence of osteoarthritis in non–weight-bearing areas, including finger joints, it has been suggested that factors such as adipokines, one representative of this family being leptin, could promote cartilage damage, thus inducing osteoarthritis.15,16 Therefore, although mechanical factors may be one element favoring the development of osteoarthritis in obese patients, inflammatory mediators also appear to be important contributing factors. Thus, in addition to weight loss, additional treatments may eventually be required for optimal therapeutic intervention.

Orthotic devices
Orthotic devices such as special footwear, insoles, knee bracing, and canes are recommended for patients with hip and/or knee osteoarthritis.5,17 The latest ACR guidelines recommend medially-directed patellar taping, as well as medially-wedged insoles for patients with lateral compartment knee osteoarthritis, and laterally-wedged subtalar strapped insoles for those with medial compartment knee osteoarthritis.1 Canes held in the contralateral hand as a walking aid can reduce pain in patients with hip and knee osteoarthritis. In knee osteoarthritis, use of braces’ and sleeves was shown to have beneficial effects compared with medical treatment alone (acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs]), as assessed by the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and function tests.16 Moreover, braces seem to be more effective than sleeves, and laterally-wedged insoles may decrease NSAID intake compared with neutral insoles.18

Alternative therapies
Acupuncture6 and transcutaneous electrical stimulation17 have been reported to show some short-term pain relief efficacy, and they are considered alternative strategies for the management of osteoarthritis. These strategies are conditionally recommended by the ACR guidelines for those patients with knee osteoarthritis who are candidates for total knee arthroplasty but are unwilling or unable to undergo surgery because of comorbidities or concomitant medications contraindicating such surgery.1

Pharmacological treatment
The prescribing habits of physicians have changed over time. Because osteoarthritis is a chronic disease and is more common in people aged over 60 years, safety remains critical. Guidelines for the medical management of osteoarthritis fo-
Focus on controlling pain and improving function and quality of life while minimizing therapeutic toxicity (see Table I for an overview of the adverse effects of the different pharmacological treatments available).2,3,17 For hand osteoarthritis, the recent ACR guidelines recommend topical capsaicin, topical NSAIDs, oral NSAIDs including cyclooxygenase (COX)-2 inhibitors, and tramadol.1 They also advise against the use of opioids or intra-articular treatments for this condition. For knee and hip osteoarthritis, acetaminophen, oral NSAIDs, topical NSAIDs (except for hip osteoarthritis), tramadol, and intra-articular steroid injections are recommended.1

**Symptomatic treatments**

**Oral analgesics**

Acetaminophen remains the first-line therapeutic agent for mild-to-moderate pain2,3,17 because of its low cost and its efficacy and safety profile for doses not exceeding 4 g per day (although a maximum of 3 g is more advisable, in line with US Food and Drug Administration recommendations). If found to be successful at alleviating pain, it is recommended that acetaminophen be the preferred long-term oral analgesic.2 It has been reported that acetaminophen is less effective at relieving osteoarthritis pain than NSAIDs18 but more effective than placebo.19 However, this result was not confirmed by a study using WOMAC and the Lequesne index to assess efficacy.20 The use of analgesics in osteoarthritis should take into account the clinical context, however. Significant adverse effects have been reported with acetaminophen, including gastric ulcerations and bleeding, increased risk of mild loss of renal function with long-term consumption, and hypertension with doses of up to 3 g per day.21-23 Furthermore, even at therapeutic doses, acetaminophen can cause asymptomatic elevation of liver enzymes in healthy people.24 The implications of this remain unclear, but it is recommended that acetaminophen should not be used in patients with existing liver dysfunction or related risk factors. On the basis of the aforementioned information, it is recommended that the lowest effective dose of acetaminophen be used for pain relief.

NSAIDs are generally recommended for patients who are unresponsive to appropriate dosages of acetaminophen. These should be prescribed at the lowest dose and for the shortest possible duration,17 and preferentially for inflammatory flares. According to the new ACR guidelines,1 NSAIDs should be used for the initial management of hand, hip, and knee osteoarthritis, as with acetaminophen and tramadol. Moreover, for patients aged over 75 years, rather than prescribing oral NSAIDs, guidelines recommend the use of topical NSAIDs, duloxetine, tramadol, or intra-articular hyaluronan injections. In patients suffering from upper gastrointestinal ulcers without any gastrointestinal bleeding in the prior year, for cases where the physician chooses to prescribe an NSAID, the ACR and Osteoarthritis Research Society International (OARSI) guidelines recommend the use of either a COX-2 inhibitor rather than a nonselective NSAID, or a nonselective NSAID combined with a proton-pump inhibitor.1,17 For patients with reports of gastrointestinal bleeding within the past year, the use of a COX-2 inhibitor in association with a proton-pump inhibitor is recommended.1 Although NSAIDs are known to be superior to acetaminophen for pain relief,19 their use is limited by a number of adverse effects, including gastrointestinal, renal, and cardiovascular adverse effects, which increase with

<table>
<thead>
<tr>
<th>Treatment type</th>
<th>Adverse effect/safety profile</th>
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<tbody>
<tr>
<td>Oral</td>
<td>Acetaminophen: GI discomfort, bleeding; renal failure; hypertension; hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>NSAIDs; coxibs: GI ulcer/bleeding; cardiovascular events; renal events</td>
</tr>
<tr>
<td></td>
<td>Opioids: Constipation; vomiting; somnolence; increased risk of fracture, morbidity, and mortality in elderly</td>
</tr>
<tr>
<td></td>
<td>Duloxetine: Constipation; nausea; hyperhidrosis</td>
</tr>
<tr>
<td>Topical</td>
<td>Topical NSAIDs: Skin reactions; GI events</td>
</tr>
<tr>
<td></td>
<td>Capsaicin: Skin burning sensation; long-term skin desensitization?</td>
</tr>
<tr>
<td></td>
<td>Lidocaine patches</td>
</tr>
<tr>
<td>Injectable</td>
<td>Intra-articular corticosteroids: Local infection, systemic effects</td>
</tr>
<tr>
<td></td>
<td>Intra-articular hyaluronic acid or viscosupplementation: Local reactions at the site of injection, swelling, flares of pain</td>
</tr>
</tbody>
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<tr>
<th>Slow-acting symptomatic drugs</th>
<th>Adverse effect/safety profile</th>
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</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Glucosamine and chondroitin sulfate: Lower GI effects</td>
</tr>
<tr>
<td>Diacerein</td>
<td>Avocado soybean unsaponifiables</td>
</tr>
</tbody>
</table>

**Table I. Adverse effects of different pharmacological options for the treatment of osteoarthritis.**

Abbreviations: GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.
The risk level varies according to the drug and dosage. COX-2 inhibitors were shown to be as effective as conventional NSAIDs for pain relief, with fewer gastrointestinal complications, but with a potential cardiovascular risk—which is also shared by conventional NSAIDs. Physicians should therefore take into account their patients’ comorbidities and assess their individual global risk before prescribing NSAIDs.

In recent years, opioids have become a widely prescribed class of drugs, especially for osteoarthritis patients who either have contraindications or an intolerance to NSAIDs or who have failed to respond to both acetaminophen and NSAID treatment. Opioids are recommended by the new ACR guidelines for patients with symptomatic knee osteoarthritis who have not had an adequate response to nonpharmacological or pharmacological modalities and are either unwilling to undergo or are not candidates for total joint arthroplasty. However, opioids are not recommended for the management of hand osteoarthritis–related pain. It is common to start with a weak opioid such as codeine or tramadol, often in combination with acetaminophen, and if ineffective or not tolerated, to use a stronger opioid like hydrocodone, oxycodone, morphine, or transdermal fentanyl. However, adverse events are frequent and significant, and include sedation, constipation, urinary retention, nausea and vomiting, respiratory depression, and confusion. Impaired coordination and judgment can lead to falls, particularly in older adults who are more susceptible to opioid-related effects as a result of renal insufficiency and/or lower lean body mass. In elderly people, opioids may cause severe injuries from falls, such as hip fractures, or even death. Fracture risk appears to be greater with opioids than with NSAIDs in older people, and the risk increases with higher opioid dosage, especially during the first 2 weeks after initiating short-term opioid therapy. Moreover, it seems that opioids do not improve patient functioning or quality of life.

Patients with osteoarthritis have been shown to have higher mortality than the general population, particularly because of cardiovascular events. This appears to be strongly related to walking disability and reduced physical activity. Thus, immobility resulting from osteoarthritis may shorten lifespan. One may wonder if opioids, by reducing patient mobility, may reduce life expectancy by increasing cardiovascular risk. However, this relationship has not yet been established. The use of opioids in a chronic and painful disease such as osteoarthritis is still controversial for many reasons. It is recommended that opioid treatment be started at a low dose and gradually adjusted upwards, taking into account renal function, age, and other relevant risk factors. Long-term opioid use should be avoided or at least regularly reevaluated. The benefits of using opioids should be weighed as judiciously as possible. For the past few years, antidepressants have been used in chronic pain management because of their reported analgesic action, which is independent of their antidepressive effect. In recent years, the chronic pain often observed in osteoarthritis has been shown to involve centrally-mediated pain pathway dysfunction, which has led to the study of drugs that have a centrally-mediated action. Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor with central nervous system activity that is already used in three chronic pain conditions: diabetic peripheral neuropathic pain, fibromyalgia, and chronic low back pain. Recently, duloxetine was found to improve pain as well as function in knee osteoarthritis, as evaluated by clinically relevant outcomes in two 13-week trials.

The drug’s effect is related to a direct analgesic effect, independent of improvement of depression and anxiety. The main adverse events reported included nausea, constipation, and hyperhidrosis. Duloxetine is recommended by the ACR guidelines as an alternative treatment for patients with symptomatic knee osteoarthritis who have failed to respond to both pharmacological and nonpharmacological options. Controlled trials to compare duloxetine with other interventions in osteoarthritis and to evaluate its efficacy in combination with other therapies may be useful to potentially enhance treatment options.

**Topical treatments**

Adjuvant topical therapies are interesting treatments that can be used to decrease the consumption of analgesics. Topical NSAIDs, such as diclofenac and ketoprofen, seem to be as effective as oral NSAIDs but with a lower risk of systemic exposure and gastrointestinal complications. Their principal reported adverse effect is local skin reactions. They are recommended as alternative or adjuvant therapy, although ACR guidelines recommend them for the initial management of knee osteoarthritis and prefer them to oral NSAIDs for patients older than 75 years of age.

Capsaicin, the active principle ingredient of hot chili peppers, can cause depletion of substance P from sensory nerve endings and reduce or abolish the transmission of painful stimuli. However, its effectiveness and safety in pain relief remains controversial. A burning sensation is the most common adverse effect, particularly during the first week of application. It is still unclear if long-term capsaicin treatment can cause persistent desensitization of the skin that may not be totally reversible. Capsaicin is recommended by guidelines for the initial management of hand osteoarthritis, but not knee osteoarthritis.

Lidocaine patches, which are approved for postherpetic neuralgia, have also been reported to reduce neuropathic pain associated with moderate to severe osteoarthritis of the knee, without any reported treatment-related adverse effects.

**Injectable therapies**

Intra-articular injection of a long-acting corticosteroid is recommended for relief of pain from osteoarthritic flares, especially if accompanied by effusion and when NSAIDs are ineffect-
The ACR guidelines recommend intra-articular corticosteroid injections for the initial management of knee and hip osteoarthritis. Short-term pain reduction in knee osteoarthritis occurs after 2 to 3 weeks, but has no significant effect on function. The Cochrane Database of Systematic Reviews reported that after 4 weeks, there was no effect on pain, physical function, or stiffness. However, repeated injections of intra-articular corticosteroids every 3 months for 2 years showed pain relief efficacy after 1 year but not after 2 years. The long-term safety of repeated intra-articular steroid injections in symptomatic knee osteoarthritis has been demonstrated, with improvement of osteoarthritis symptoms for up to 2 years. Comparisons between corticosteroids have revealed that triamcinolone hexacetonide is superior to beta-methasone.

Viscosupplementation could have a significant benefit for knee osteoarthritis, despite some reported local acute reactions such as transient pain and swelling at the injection site. Viscosupplementation is recommended by guidelines for knee osteoarthritis, and compared with intra-articular corticosteroids, it shows delayed but prolonged efficacy. The OARSI guidelines consider that intra-articular hyaluronate injections may be useful for the treatment of knee osteoarthritis and have a beneficial symptomatic effect. Moreover, the ACR guidelines conditionally recommend viscosupplementation for patients who have had an inadequate response to initial therapy. By contrast, a single injection of hyaluronic acid in hip osteoarthritis seems to be no more effective than placebo.

More data are needed on the structural effect of viscosupplementation.

**Symptomatic slow-acting drugs for osteoarthritis**

Disease-modifying agents that not only reduce joint pain but also slow progression of the disease are of interest for alleviation of the manifestations of osteoarthritis over the long term. For the past 10 years, chondroitin sulfate and glucosamine sulfate have been widely prescribed and used by osteoarthritis patients for symptom relief. They are safe, and have possible structure-modifying effects. Glucosamine is a naturally occurring amino monosaccharide, and chondroitin sulfate belongs to the group of glycosaminoglycans and is a major component of the articular cartilage.

In osteoarthritis clinical trials, the symptomatic effect size of glucosamine varies and is considered controversial. However, the results of studies have greatly depended on the different products used, the study population, and study design and quality. Formulations of glucosamine that result in lower plasma concentrations and potential low bioavailability, as well as study populations with a low baseline level of pain, may have contributed to the controversy. Glucosamine sulfate and chondroitin sulfate have been approved as drugs for the treatment of osteoarthritis in Europe, but not in North America, where they are regulated not as drugs but as nutraceuticals. As a consequence, substantial variation in their content is possible. This explains why in the latest ACR guidelines, these agents were not recommended for treatment of osteoarthritis. Glucosamine sulfate was found to be effective as an osteoarthritis pain relief treatment and for improvement of function. Recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system concluded that glucosamine sulfate demonstrated pain reduction and improvement in physical function with very low toxicity and with moderate-to-high-quality evidence. The latest OARSI guidelines recommend the use of glucosamine sulfate and chondroitin sulfate for osteoarthritis treatment, as they demonstrated pain relief with a moderate to large effect size (0.58 and 0.75, respectively). When a purified preparation of glucosamine sulfate is used, it appears to be safe—in particular, with no induction of glucose intolerance in healthy adults. The protective effect of glucosamine sulfate on structural progression of knee osteoarthritis was reported in two studies exploring the radiological progression of knee osteoarthritis after daily administration of glucosamine sulfate for 3 years. Chondroitin sulfate has been shown to improve knee joint swelling and delay radiographic progression in patients with knee osteoarthritis evaluated by x-rays, and more recently a magnetic resonance imaging study reported that chondroitin decreases cartilage loss and the progression of bone marrow lesions. A recent post-hoc analysis of an osteoarthritis clinical trial reported a trend favoring chondroitin sulfate versus placebo for delayed occurrence of total knee replacement at 4 years. However, the structural effects of glucosamine and chondroitin sulfate remain under debate, and these treatments are not registered as structure-modifying agents.

Diacerein, an inhibitor of interleukin-1β, is a slow-acting agent with pain-relieving symptomatic effects in patients with knee osteoarthritis, and which also reduces the progression of hip osteoarthritis. Diacerein provides sustained pain relief for several weeks after discontinuation, suggesting a long carry-over effect, and an analgesic-sparing effect. Moreover, the effect of diacerein has been found to be additive to that of NSAIDs. Interestingly, it does not inhibit cyclooxygenase or prostaglandin E2. Loose stools and diarrhea are the most frequent adverse events. It is safer for the upper gastrointestinal system than NSAIDs and has a good overall safety profile, and it is therefore an alternative option to NSAIDs for the treatment of osteoarthritis.

Avocado soybean unsaponifiables (ASU) are fractions of unsaponifiable avocado and soybean oils. The symptomatic efficacy of ASU has been assessed in patients with hip and knee osteoarthritis. ASU seems to be effective at pain reduction and has shown some beneficial effects on clinical symptoms of knee and hip osteoarthritis, with a carry-over effect that persists after treatment discontinuation. A recent study reported that in hip osteoarthritis, a 3-year treatment with ASU reduced the percentage of joint space width progressors, indicating a potential structure-modifying effect.
Surgical treatment

Initial treatment of osteoarthritis should be conservative. However, when pain and loss of function persist after the use of appropriate nonpharmacological and pharmacological treatments, surgery should be considered to reduce disease morbidity. Surgical options for knee osteoarthritis are arthroscopy, including lavage and debridement (the efficacy of which is controversial), cartilage repair surgery (bone marrow stimulating techniques, transplantation of osteochondral grafts), osteotomy with axis correction, and arthroplasty (unicondylar knee arthroplasty [UKA] and total joint replacement).

Arthroscopy is a minimally invasive surgical technique used for chondral surface debridement, lavage of joints, removal of torn meniscal fragments, and repair of menisci and cruciate ligament injuries. It remains controversial because it usually provides a short-term benefit and does not seem to delay progression to joint replacement.

Arthroscopy should be of interest for selected patients such as those with symptomatic meniscal disease.
tears, in whom it can be used to remove the degenerative fragments and alleviate mechanical symptoms. Bone marrow stimulation through the use of a microfracture technique induces subchondral injury and bleeding that may promote chondrogenesis by mesenchymal stem cells in the defective area. Its efficacy is uncertain, however, because of variability in the volume of cartilage repair that has been achieved, as well as possible functional deterioration.62

Patients with unicompartmental osteoarthritis of the knee can be treated with a correction osteotomy17 or unicompartmental or total knee arthroplasty (TKA). Osteotomy can be considered when knee osteoarthritis is associated with valgus or varus deformation. It transfers load-bearing from the pathological compartment of the knee to the normal compartment in order to reduce pain and delay joint replacement. Nevertheless, its longevity is limited, and conversion to total knee replacement often occurs within the following few years. UKA seems to be as safe and effective for pain relief and functional improvement as TKA, as well as high tibial osteotomy in patients with unicompartmental knee osteoarthritis.63 Long-term survival rates with UKA are variable but are reported to be around 90% at 10 years, which is less than for TKA (up to 98% at 15 years), except in younger patients.61 TKA remains a success-

<table>
<thead>
<tr>
<th>Treatment type</th>
<th>Intervention</th>
<th>OARSI effect size* (95% CI)</th>
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<tbody>
<tr>
<td>Nonpharmacological</td>
<td>Education</td>
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</tr>
<tr>
<td></td>
<td>Exercise</td>
<td></td>
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<tr>
<td></td>
<td>Strengthening for knee</td>
<td>0.06 (0.03, 0.10)</td>
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<tr>
<td></td>
<td>Aerobic for knee</td>
<td>0.32 (0.23, 0.42)</td>
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<tr>
<td></td>
<td>Exercises for hip</td>
<td>0.52 (0.34, 0.70)</td>
</tr>
<tr>
<td></td>
<td>In water for hip and knee</td>
<td>0.38 (0.08, 0.68)</td>
</tr>
<tr>
<td></td>
<td>Prevention of injuries</td>
<td>0.19 (0.04, 0.35)</td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
<td>0.20 (0.00, 0.39)</td>
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<td></td>
<td>Orthotic devices</td>
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<td>Acetaminophen</td>
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<td>NSAIDs and COX-2 inhibitors</td>
<td>0.29 (0.22, 0.35)</td>
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<td>Opioids</td>
<td>0.78 (0.59, 0.98)</td>
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<td>Duloxetine</td>
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<td>Topical NSAIDs</td>
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<td>Capsaicin</td>
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<td>Lidocaine patches</td>
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<td></td>
<td>Injectable</td>
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<tr>
<td></td>
<td>Intra-articular corticosteroids</td>
<td>0.58 (0.34, 0.75)</td>
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<td>Intra-articular hyaluronic acid or viscosupplementation</td>
<td>0.60 (0.37, 0.83)</td>
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<td>Symptomatic slow-acting osteoarthritis drugs</td>
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<tr>
<td></td>
<td>Oral</td>
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<tr>
<td></td>
<td>Glucosamine sulfate</td>
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<td>Chondroitin sulfate</td>
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<td></td>
<td>Diacerein</td>
<td>0.24 (0.08, 0.39)</td>
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<tr>
<td></td>
<td>Avocado soybean unsaponifiables</td>
<td>0.38 (0.01, 0.76)</td>
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<th>Intervention</th>
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<tr>
<td>Surgical</td>
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<td></td>
<td>Osteotomy with axis correction</td>
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<tr>
<td></td>
<td>Arthroplasty (UKA, TKR, THR)</td>
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*An effect size of 0.2 is considered small, while 0.5 is considered moderate, and >0.8 is considered large.

Table III. Multimodal management of osteoarthritis and effect size of the different components of the 2010 guidelines from Osteoarthritis Research Society International (OARSI).

Abbreviations: CI, confidence interval; COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug; THR, total hip replacement; TKR, total knee replacement; UKA, unicompartmental knee arthroplasty.

ful treatment for end-stage symptomatic knee osteoarthritis, especially in elderly patients. The main complications are persistent postoperative pain (especially in the femoropatelar compartment), infections, and stiffness of the knee. In order to improve outcomes with TKA, computer-assisted navigation and minimally invasive techniques are being developed.

The choice of surgical treatment may be based on level of pain and physical function, disease stage, patient age, and comorbidities. No specific cut-off point defining the requirement for joint replacement currently exists.64 However, the aim of a surgical intervention for osteoarthritis such as joint replacement should be to restore patient mobility and give the patient enough capacity to perform the level of activity required to help prevent cardiovascular diseases.

References
37. Gambotti AR, Galer BS, Ondarco R, Jensen MR, Argoff CE. Lidocaine patch 5% and its positive impact on pain qualities in osteoarthritis: results of a pilot

Conclusion
Clinicians managing osteoarthritis are able to draw upon a wide spectrum of therapeutic options, combining nonpharmacological approaches and pharmacological treatments both to relieve pain and to attempt to delay disease progression (Figures 1 and 2; Table II, page 177), as recommended by the OARSI (Table III) and ACR guidelines. The trade-off between benefits and adverse effects should always be considered when choosing an appropriate treatment from among the available agents. The current therapeutic options, however, are neither exclusive nor sufficient. Thus, the focus is moving toward developing disease-modifying osteoarthritis drugs that can be taken in association with conventional therapeutic strategies to provide more effective treatment of osteoarthritis.
Osteoarthrite: une histoire de relations étroites


Keywords: analgesic; chondroitin sulfate; exercise; glucosamine sulfate; guideline; intra-articular; osteoarthritis; weight loss; surgery

TREATEMENTS OF THE ARTHRITIC: WHERE DO WE STAND AT THE MOMENT?

L’arthrose, la forme la plus courante des pathologies articulaires, entraîne douleur et diminution de la qualité de vie. Actuellement, pour cette maladie, plusieurs médicaments symptomatiques sont commercialisés. Cependant, il n’existe à ce jour aucun traitement prévenant la détérioration articulaire. Dans cet article seront décrits les traitements non pharmacologiques et pharmaco-logiques disponibles dans la prise en charge de l’arthrose, ainsi que les traitements chirurgicaux possibles. Les recommandations actuelles de l’Osteoarthritis Research Society International et de l’American College of Rheumatology suggèrent une approche multidimensionnelle, associant des traitements non pharmacologiques et pharmaco-logiques. La prise en charge non pharmacologique de l’arthrose repose essentiellement sur l’éducation du patient, l’exercice physique, la prévention des blessures, la perte de poids lorsqu’elle est nécessaire et l’utilisation d’orthèses. Les traitements pharmaco-logiques axés sur la réduction des symptômes comprennent les analgésiques tels que l’acétylamophène, les anti-inflammatoires non stéroïdiens (AINS), les opioïdes, la duloxétine, les AINS locaux, la paracétamol, les patchs de lidocaïne, les injections intra-articulaires de corticoïdes et d’acide hya-luronique, et les médicaments d’action lente comme la glucosamine et la chondroïtine sulfate, la diacéréhine et les insaponifiables d’avocat et de soja. Le traitement chirurgical est envisagé lorsque les approches non pharmaco-logiques et pharmaco-logiques visant à réduire les symptômes ont échoué.
Osteoarthritis (OA) affects hundreds of millions of people worldwide and is responsible for a huge burden of pain, functional limitations, and loss of quality-adjusted life expectancy. OA of the knee accounts for more than 90% of total knee replacements (TKR). By 2030, the incidence of TKR in the US is expected to increase by more than 6-fold. Pain and difficulty walking limiting participation in daily activities are the primary reasons for undergoing TKR. However, among patients with disabling OA, only a minority are willing to consider TKR. Reduced willingness to undergo TKR is associated with increasing age, being black (in the US), overestimation of the pain and disability needed to warrant TKR, and rejection of the medicalization of OA. The perception of the benefits of TKR is less positive among women and those of lower socioeconomic status. TKR is one of the most cost-effective medical interventions. Data from joint registries show that the 10-year reoperation rate for TKR is less than 5%. However, between 10% and 30% of patients undergoing TKR report little or no improvement following surgery, or are not satisfied. Patients’ expectations of joint replacement are relief of pain and improved mobility. Following TKR, the expectations regarding pain relief, walking ability, and the ability to perform daily activities are fulfilled to a greater extent than the expectations of being able to perform more physically demanding activities. To ensure optimal patient satisfaction, health professionals should provide sufficient information so that patients have realistic expectations of the results of TKR.

Medicographia. 2013;35:181-188 (see French abstract on page 188)
OA most commonly affects the knees, hips, and hands, but may affect other joints as well, such as the shoulders, elbows, ankles, feet, and spine. The prevalence rises steeply between the ages of 50 and 60 for both women and men, so that the majority of patients with symptomatic OA are aged between 60 and 80 years. However, OA also occurs in younger and middle-aged patients. In fact, effective treatment of OA represents a particularly difficult challenge in patients aged between 30 and 60 years.

OA of the knee represents a major share of the OA disease burden, and OA is by far the most common reason for total knee replacement (TKR), usually accounting for more than 90% of knee replacement procedures. The incidence of TKR for OA is rising steeply, and should continue to rise dramatically, with a more than 6-fold increase expected by 2030 in the US. The following discussion will focus on knee replacements for OA, but will also, where appropriate, use evidence gathered from the study of hip replacement for OA.

Risk factors for knee OA
OA of the knee shares the same general risk factors as OA of the other joints in that each patient and each joint carries its own mix of genetic and environmental factors responsible for the development of OA. For the knee, individual genetic variability is thought to account for about 40% of the risk, with environmental factors accounting for the remaining 60%. Genetic variability may, for example, be expressed as individual differences in the quality of the cartilage matrix, reactivity of inflammation pathways, growth and repair pathways, and joint shape. Environmental risks are mostly biomechanical, affecting the dynamic loading of the joints and increasing stress on joint tissues. This in turn will result in the activation of inflammation and tissue degradation. Leading examples of such environmental “joint stressors” are overweight and obesity, joint injury, and occupational overload. Genetically determined variations in joint shape may also influence the risk of OA by increasing joint stress.

Epidemiology of knee OA
As already stated, the disease burden of OA is enormous. It is the most common form of progressive joint disease, and affects 50 million adults in the US and Europe, with OA of the knee representing a major share of this burden. In the US, knee OA accounts for more than 10 million quality-adjusted years of life lost, and almost 1 million hospital admissions per year. Although knee OA is usually perceived as a disease of the elderly, the mean age at diagnosis is actually 56 years. The prevalence of knee OA is rising due to the aging of the population and increasing rates of joint injury and, most importantly, obesity.

Management options for knee OA
A wide range of treatments are used for knee OA, including nonpharmacological, pharmacological, and surgical approaches. OA management strategies are determined by disease severity, patient preferences, local resources, and established treatment modalities.

A stepwise approach to the management of osteoarthritis is widely recommended, starting with patient empowerment and self-management, and, if these simple approaches are unsuccessful, the addition of specific medical or surgical interventions (Figure 1). With the exception of knee replacement, the effect size for most therapeutic interventions in knee OA is only small to moderate.

Basic management of osteoarthritis includes education, exercise, and weight loss (for overweight people), which can be complemented as needed by simple analgesics, and, for hand and knee joints, topical nonsteroidal anti-inflammatory drugs (NSAIDs). Additional studies are needed to tailor the different programs to different patients. Common sense suggests that a combination of treatments benefits most patients.

Oral NSAIDs and paracetamol (acetaminophen) are often used by patients with OA. However, gastrointestinal, renal, and cardiovascular side effects are of particular concern with NSAIDs, since many patients with OA are elderly and have comorbidities, and thus are at increased risk of some or all of these side effects. These concerns add complexity to the task of pre-
scribing pain relievers for patients with OA. The utility of opioids for OA is limited by their side effects. Corticosteroid injections are frequently used, but their benefit is short-lived (1 to 4 weeks). In addition to these treatments, patients with knee OA use a wide range of alternative therapies.

The surgical management of knee OA commonly includes arthroscopic surgery of the knee upon suspicion of a meniscus tear or cartilage derangement amenable to surgical treat-

ment. However, high-quality trials comparing arthroscopic surgical debridement (including meniscus resection) with sham surgery, medical care as usual, or exercise programs found no difference between the groups compared,15-18 thereby showing that arthroscopic surgery is of no added benefit for these patients. Over the age of 35, meniscus lesions are often part of the early stages of the osteoarthritic process, and the diagnosis of a meniscus tear by magnetic resonance imaging (MRI) of the osteoarthritic knee does not correlate with the presence of symptoms.19

Valgus osteotomy of the tibia can provide long-lasting pain relief and functional improvement in physically active patients of less than 60 years of age in whom OA is mainly limited to the medial knee compartment. If and when needed, the osteotomy can later be converted to a knee replacement. In a large national Swedish series of about 3000 patients who had undergone tibial osteotomy for knee OA at a mean age of 52 years, the 10-year “conversion rate” to TKR was 30%.20 This suggests that osteotomy should remain a viable option for patients in this group, thereby delaying or obviating the need for knee replacement by more than 10 years in most cases.

Practice variations in the use of knee replacement and future projections for TKR use

Joint replacement for OA of the knee may be the only intervention with a large effect size, but it is only appropriate for patients with advanced disease or substantial symptoms that do not respond to other treatments. This group is but a minority of all those with knee OA, but still represents a very substantial number of patients. Rates of TKR are increasing worldwide, and in 2010, more than 600 000 procedures were carried out in the US alone, with rates tripling over the last decade in those aged between 45 and 64.9,21 At over $20 000 per procedure, the annual cost of TKR in the US now exceeds $13 billion.5,22,23

National knee replacement registry data from the Scandinavian countries, UK, and Australia also confirm the continuous and rapid increase in the incidence of knee replacement for OA. For example, results from the Swedish Knee Arthroplasty Register show that the annual rate of primary TKR for OA in Sweden doubled between 2000 and 2010 (Figure 2), while the annual rate of TKR in those younger than 55 increased 5-fold.24,25 The dramatic increase seen in younger patients may in part reflect a change in surgical practice from the use of osteotomy and unicompartmental knee replacement to TKR in younger patients.25

The mean age for TKR has changed over time, and in Sweden it now shows a decreasing trend, being about 69 years for both women and men (Figure 3, page 184).24 Reflecting the current routine widespread use of TKR as a procedure to treat severe knee OA, 1 in 14 elderly women in Sweden has
now had a TKR. 24 Similarly, nearly 1 in 20 Americans over 50 years of age have had knee replacement surgery, which represents more than 4 million people.9,21

Direct comparisons of the rates of TKR for OA between different countries are hindered by the limited availability of high-quality specific data for OA procedures, as well as by differences in population structure. The 2007-2009 estimated rates of primary TKR for all diagnoses per 100 000 people varied between 9 for Romania and 213 for the USA.26 Even between countries with seemingly similar socioeconomic conditions, national health care systems, and population structures, the TKR rates per 100 000 varied greatly, ranging from 188 for Germany, 178 for Finland, 112 for Sweden, to 98 for France.26 The reasons for these wide variations in usage are not clear, but are likely to be due to differences on both the “supply side” (health care services) and the “demand side” (patients).

Time-related trends in TKR use
The projections for future TKR rates have regularly been outdone by reality. In the US, the demand for primary TKR was, in 2005, expected to grow by more than 600%, to reach 3.48 million procedures by 2030.27 The growth of total knee revision surgeries was projected to be proportional, with the demand for revision procedures expected to double between 2005 and 2015. If these predictions hold true, both health care infrastructures and the training of orthopedic surgeons will need to expand accordingly. The dramatic increase in TKR rates inevitably leads to questions about financial feasibility in the future: who will pay? So what are the possible reasons for the steeply increasing demand for TKR seen over the last decade? The reasons for this increase are most certainly multifactorial. Population growth, the increasing number of elderly people, and the increase in average body mass index (BMI) are, no doubt, important factors.

The increase in the age-standardized prevalence of knee OA (for which there is limited evidence) may be driven by the now global epidemic of overweight and obesity (for which there is strong evidence), and by an increase in joint injury rates. These two “environmental” risk factors may together be responsible for up to 50% of knee OA cases in some societies.21 The importance of overweight and obesity in the risk of severe knee OA leading to TKR was investigated in a prospective population-based cohort study (Figure 4); a mean BMI of 30 was associated with an 8-fold increase in TKR risk when compared with a “normal” BMI of about 22.28 Even an increase in BMI from 21-22 to 24-25 (ie, within a BMI range that is considered normal) was associated with a 3-fold risk increase in the rate of TKR for OA. In fact, in this large population-based study, very few TKR procedures were carried out on patients in the lowest BMI quartile (Figure 4). In the US, the major impact of obesity on the risk of knee OA and TKR can also be illustrated by estimating the number of TKRs averted by “reversing” the prevalence of obesity to the levels of 10 years ago. This would correspond to a mean BMI reduction of 0.6 or a reduction in body weight of less than 2 kg for a person of average height. This means that more than 100 000 TKRs would be averted over the remaining life span of this population.2
among women than men, and among those of lower socioeconomic status. Although blacks suffer from more severe OA than whites in the US, they are less likely to consider surgery as a solution to their problem, and this is associated with less positive beliefs about the benefits of surgical procedures. A person’s knowledge and beliefs regarding TKR appears to be largely shaped by his or her interactions with family and friends. The differences summarized here may at least in part explain the inequities observed in joint disease care.

Given the low proportion of patients with OA in whom TKR is indicated who are actually willing to undergo the procedure, changes in willingness to undergo TKR seem to be an important contributing factor in driving the recent increase in the incidence of TKR, and also in driving a future increase in the demand for TKR. Increased expectations regarding the maintenance of an active lifestyle into older age may influence willingness, as may direct-to-consumer advertising, which is now common in many countries. Studies investigating temporal changes and changes in willingness to undergo TKR in different settings would be of considerable interest.

**Indications for TKR as perceived by health professionals and patients**

Several attempts have been made to develop consensus criteria for TKR indications. As in all such efforts, the composition of the group and the method used to form the consensus determine the result. Well-known examples of such criteria are those developed in New Zealand and Canada. Components of these scores include pain, functional impairment, problems in care giving, and radiographic severity. However, attempts to determine cut-off points leading to an “appropriate” indication for TKR by correlating preoperative patient-reported symptoms with recommendations for placement on a TKR waiting list have not been successful. This suggests that these more easily measured components explain only a minor proportion of the decisions to place patients on waiting lists for surgery.

Most TKR criteria have been dominated by the views of health professionals, often orthopedic surgeons. The views of patients on the appropriateness of TKR have been explored to some extent, and suggest that they do not always agree with the views of health professionals. The concept of the “capacity to benefit” from TKR suggests that the benefits should outweigh any likely risks or unintended consequences by a considerable margin for TKR to be indicated.

**Effectiveness of knee replacement: what determines outcome and patient satisfaction after TKR for OA?**

It has been said that total joint replacement “doesn’t bring years to life, but brings life to years.” This is true in the sense that patient-reported outcomes of joint replacement are on
average “good to excellent,” and it is particularly pertinent in comparison with most nonsurgical treatments for severe OA. The Scandinavian national joint registries have for many years reported on the continuous improvement of outcomes over time as a result of improved surgical, anesthesiological, and care procedures and materials. In Sweden, the 10-year revision (reoperation) rate is now estimated to be less than 5% for patients operated with TKR for OA at the beginning of this century. This means that for more than 95 out of 100 patients undergoing TKR for OA, the patient will be survived by the implant. Reoperation rates from other countries have generally been somewhat higher, perhaps because of the choice of implants, surgical techniques, and other factors. However, it is well-known that the risk of reoperation is considerably higher for younger patients operated with TKR, than for older patients. Higher revision rates for younger patients operated with TKR are expected in light of the changing demographics of TKR surgery, with rapidly increasing numbers of younger patients undergoing joint replacement. The Swedish national registry reports no difference in revision rates between men and women operated with TKR for OA in the 2000s.

When considering these excellent results, it should be noted that they represent reoperation rates, not patient-reported outcomes. In fact, between 10% and 30% of patients undergoing joint replacement report little or no improvement following surgery, or are not satisfied with the outcome. Factors associated with a less than optimal patient-reported outcome of TKR at 6 months include worse preoperative pain and function, increased anxiety/depression, and living in poorer areas. Multiple joint involvement negatively influences the outcome after TKR, while severe obesity results in slower recovery after surgery, but with no difference at 3 years.

It should be noted that the determinants of pain or function following TKR may not be the same in all studies. The most important expectations of patients undergoing joint replacement surgery are pain relief and improved mobility. It appears that at 5 years following TKR, patients’ expectations of pain relief, walking ability, and ability to perform the activities of daily living are fulfilled to a greater extent than their expectations of being able to perform more physically demanding activities. For example, 41% of patients expected to be able to perform activities such as golfing and dancing following TKR, while only 14% were in fact able to perform these activities 5 years after undergoing TKR. To ensure optimal patient satisfaction, it is important that health care professionals provide adequate information before surgery so that patients have realistic expectations of the results of TKR.

Conclusion

The expectations, results, and patient satisfaction with TKR surgery for OA summarized above reflect the current “case mix” of patients with regard to disease severity, expectations of outcome, age, and active life expectancy. TKR stands out as one of the most effective and cost-effective medical interventions. However, whether this outstanding record will be upheld or not given the changing demographics of patients undergoing this type of procedure, with those aged between 45 and 64 years being the most rapidly increasing group, remains to be seen. Innovations and new implant designs have at times been introduced before evidence of their efficacy and safety could be established. Improved regulatory and clinical processes for the introduction of new devices are badly needed.

Another pressing question is that of health economics. The projected dramatic increase in TKR use, if it becomes a reality, will demand increased orthopedic and hospital resources, among others, and this will result in sharply increased costs for patients and society.

References


**Keywords:** indication; osteoarthritis; total joint replacement; willingness

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**Knee replacement for osteoarthritis: facts, hopes, and fears – Lohmander**

**Prothèses de genou pour l’arthrose : réalité, espoirs et craintes**

L’arthrose touche des centaines de millions de personnes dans le monde. Elle est responsable de douleurs, de restrictions fonctionnelles et de perte d’espérance de vie ajustée sur la qualité. L’arthrose du genou est la cause de plus de 90% des prothèses totales de genou (PTG). D’ici à 2030, l’incidence des PTG aux États-Unis devrait être multipliée par 6. Les principales raisons pour la pose d’une PTG sont la présence de douleur et une difficulté à la marche limitant les activités de la vie quotidienne. Toutefois, seule une minorité de patients ayant une arthrose invalidante sont prêts à envisager la PTG. Ce faible engouement pour la pose d’une PTG est lié au vieillissement, au fait d’être Noir (aux États-Unis), à la surestimation de la douleur et du handicap nécessaires pour justifier une PTG et à un rejet de la médicalisation de l’arthrose. Les femmes et les personnes dont le statut socio-économique est bas ont une perception des bénéfices d’une PTG moins positive que les autres. Le rapport coût-efficacité de la chirurgie pour PTG est l’un des meilleurs. Les données issues des registres sur les articulations montrent que le taux de réintervention à 10 ans pour PTG est inférieur à 5%. Cependant, de 10% à 30% des patients ayant eu une PTG ne sont pas satisfaits de l’intervention, ou n’ont perçu, au mieux, qu’une amélioration modérée. Ce qu’attendent les patients d’une prothèse, c’est le soulagement de leur douleur et une mobilité améliorée. Après la pose d’une PTG, les attentes concernant le soulagement de la douleur, l’aptitude à la marche et la capacité à effectuer les activités de la vie quotidienne sont satisfaites dans une plus grande mesure que celles concernant la possibilité de pratiquer des activités plus physiques. Les professionnels de santé devraient informer les patients de façon à ce que leurs attentes soient réalistes, ce qui leur assurerait une meilleure satisfaction.
Osteoarthritis (OA) is the most common form of arthritis and represents a huge burden on both individuals and health economies. It is characterized by changes involving all the joint tissues. Affected individuals suffer pain, functional limitation, and poor quality of life. We can predict a dramatic increase in the burden of OA in aging and increasingly obese Western populations.

OA represents whole joint failure and occurs when the homeostatic equilibrium of joint tissue repair and breakdown becomes unbalanced. Risk factors for disease initiation and progression vary according to anatomical site and include age, obesity, anthropometric and anatomical characteristics, joint malalignment, and trauma. A genetic predisposition also contributes to OA risk; OA is a polygenic disease whose susceptibility results from the interaction of many genes. The mainstay of current therapy involves a combination of nonpharmacological and pharmacological interventions aimed at reducing pain and improving function. Current treatments do not inhibit structural deterioration of the OA joint; yet, the unmet need for this type of treatment is immense. The current definition of a disease-modifying OA drug (DMOAD) is that of a drug that inhibits structural disease progression and ideally also improves symptoms and/or function. There are currently no licensed DMOADs but there are many prospective agents under investigation. The challenges of DMOAD development include the establishment of appropriate preclinical animal models that reflect human OA, the limitations of the current radiographic standard for structural assessment, and the lack of stratification of patients in trials by phenotype or tissue involvement. Furthermore, DMOADs should probably be used in early disease before irreversible molecular and biomechanical pathology is established, as is commonly present at the time of diagnosis. DMOADs are likely to be prescribed for long periods in this chronic illness of an aging population, which demands excellent safety data in a target population with multiple comorbidities and the potential for drug interactions. Issues in DMOAD development, potential DMOADs, magnetic resonance imaging biomarkers, and lessons learned from the treatment of rheumatoid arthritis are briefly discussed in this review.
cral interventions aimed at reducing pain and improving function. The pharmacological interventions include paracetamol, nonsteroidal anti-inflammatory drugs, and opiate analgesics. Their utility is limited by—at best—moderate effect size, or by significant toxicities, especially as OA is most prevalent in the elderly where comorbidities are more common. Current treatments do not appear to inhibit the structural deterioration of the OA joint; the unmet need for such a treatment is immense.

**What are disease-modifying osteoarthritis drugs?**

A disease-modifying osteoarthritis drug (DMOAD) is a drug that inhibits the structural disease progression of OA and ideally also improves symptoms and/or function. There are currently no licensed DMOADs. There are draft guidelines from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) both requiring that a DMOAD should not only slow or halt radiographic structural disease progression, but also achieve patient-reported long-term clinical benefit. Typically, attempts at developing DMOADs have focused primarily on preventing hyaline cartilage loss, thereby providing putative “chondroprotective” agents. However, and perhaps appropriately, as typical clinical OA involves multiple tissues, more recent attempts have been made at targeting other tissues including the subchondral bone, which plays an important role in OA pathogenesis.

There are a number of issues to consider in developing therapies that modify structural disease progression.

**Challenges in DMOAD development**

**The current standard for structural assessment: conventional radiography**

Conventional radiography is widely available and radiographic joint space width (JSW) is the traditionally used surrogate for assessing cartilage thickness. JSW can be used for both defining and measuring structural disease progression. Manual and semiautomated methods can be used to quantify JSW from a conventional radiographic image, providing different measures such as minimum, mean, or location-specific JSW. Joint space narrowing (JSN) is used as the primary end point in DMOAD trials in OA. Although JSN is a predictor of total joint replacement, the limitations of radiographic JSN should be appreciated. Indeed, while JSN is used to define cartilage loss in knee OA, magnetic resonance imaging (MRI) studies have shown that it measures a complex construct including meniscal degeneration, meniscal extrusion, and hyaline cartilage loss.

The annual rate and variability of JSN in the natural history of OA is well described, which facilitates powering in clinical trials. However, the average annual change in JSN is approximately 0.1 to 0.2 mm per annum, with change occurring in a small group of “progressors.” The relative insensitivity to change of this surrogate measure of hyaline cartilage loss means that long trials with large numbers of patients are needed in order to adequately power a clinical study. Furthermore, the sensitivity of this measure to change may be reduced by knee repositioning variability in serial radiographic measurement of JSW, so great care must be taken in repositioning methods.

Conventional radiography does not detect early (perradiographic) OA changes in the subchondral bone, cartilage, or menisci. Typically, inclusion criteria for research trials have included patients with radiographically detectable JSN (Kellgren and Lawrence grade ≥2). While this selects a group of patients who no doubt have OA, multiple large MRI studies suggest that these patients have complex multiple tissue pathologies, with gait studies suggesting a high probability of abnormal biomechanical features, meaning that these may be patients in whom pharmacological intervention alone and aimed at a single tissue would be unlikely to modify structural deterioration. A preradiographic patient cohort with milder disease may be more likely to respond. Treatment of rheumatoid arthritis according to the concept of early disease has certainly revolutionized the management of rheumatoid arthritis.

**Magnetic resonance imaging as a potential end point**

Conventional radiography cannot capture the extent of the multi-tissue involvement in OA joints. Typically, patients with Kellgren-Lawrence grade ≥2 are recruited for DMOAD trials, but these patients may lack uniformity in terms of joint tissue involvement, and this is clinically indistinguishable. Stratifying and monitoring these tissue changes among patients would require MRI.

The advantages of MRI include the ability to examine the presence and extent of pathology in all of the individual joint tissues in OA. There is good evidence of the reliability and responsiveness of MRI cartilage morphometry in knee OA and there is some evidence of its predictive and construct validity. This includes quantitative loss of cartilage volume being a potential predictor of total knee replacement. The assessment of subchondral bone marrow lesions and synovitis in knee OA has also demonstrated good responsiveness for
semiquantitative MRI assessment. Further work is required to investigate the predictive validity and quantification of these noncartilage MRI pathologies. While MRI acquisition is, of course, more expensive and time-consuming than plain radiography, there are trade-offs in that increased responsiveness should result in fewer patients being required to demonstrate a structure-modifying effect.

MRI-based joint tissue measures of OA have not been routinely used as clinical outcome measures in structure-modification DMOAD trials. However, following the last decade of MRI-OA cohort studies and trials, a recent Osteoarthritis Research Society International (OARSI) working group recommended that MRI cartilage morphology assessment be used as a primary structural end point in clinical trials and noted the rapid evolution of quantitative MRI assessments of subchondral bone and synovium.

**Novel end points: joint arthroplasty and virtual joint arthroplasty**

While pain and function outcomes are common outcomes that may be adapted for DMOAD studies from symptom-modifying trials, less frequently used measures such as quality of life and delay in time to joint replacement may also provide important information about the value of a putative agent. Rate of joint arthroplasty has been used as an end point reflecting the severity of symptoms and structural damage, but many variables influence both the decision to perform and the timing of this outcome measure. These include the surgeon’s or physician’s opinion and the patient’s comorbidities and willingness to undergo surgery, in addition to local and national health system variations in surgical waiting lists. In an attempt to overcome these confounding factors influencing the “time to total joint replacement” end point, an alternative has been proposed. This is “time to fulfilling criteria for total joint replacement” or “virtual total joint replacement,” which could be used to evaluate treatment response to DMOADs in clinical trials. The criteria consist of a composite index of three domains: physical function, pain, and structure; its validity is currently being assessed in an international study although provisional reports indicate that large patient numbers would be required to detect differences between groups in DMOAD randomized control trials.

**Symptomatic improvement**

The current regulatory approval standard for DMOADs requires that structural disease modification be linked with some clinical benefit. However, in observational studies in OA there is generally a weak relation between pain and/or function and JSN and radiographic structural change. Furthermore, cartilage is not directly attributable as the cause of the typical OA symptoms, including pain and stiffness. Importantly, most trials of symptom-modifying drugs have been of short duration, often only 3 months long. DMOAD trials need to monitor pain over long periods of time (1 to 2 years), where the efficacy of existing analgesics has often not been clearly demonstrated. Such long-duration trials are often associated with patient drop-out, especially in an elderly population, and robust statistical modeling will be required to cope with missing data.

**DMOAD safety profile**

Prospective DMOADs for use in established OA are likely to require long-term administration in an aging population with significant comorbidities, and will thus be prescribed alongside a variety of medications. For that reason, prospective DMOADs will be required to demonstrate a good safety profile with respect to both patient tolerance and drug interactions. Long-duration trials will therefore be needed to achieve this.

**Preclinical models**

Animal models can mimic certain aspects of human disease. However, there is no single model that reflects all of the phenotypes and components of human OA. The marked differences between animal models and human disease may result in dismissing drugs that may be viable DMOADs in humans due to preclinical failure in animal models. Existing models include primary idiopathic and secondary experimentally induced disease. Small animal models may provide us with a clearer understanding of the molecular pathways involved in the pathogenesis of OA and the effects of prospective DMOADs on these pathways. Although large weight-bearing models may be more relevant, they are less frequently used. Animal models generally achieve adequate severity of OA but some may exceed that seen in humans. There is a general consensus of opinion that animal models of less severe OA will be better placed to establish the efficacy of prospective human DMOADs. Furthermore, establishing animal models with relevance to human OA will require standardization of experimental techniques, disease severity, and treatment responses.

**Are there candidate DMOADs?**

A number of prospective DMOADs are under investigation and some of those more advanced in development are summarized in Table I (page 192). The degradation of cartilage and that of subchondral bone are closely linked in OA. Table I describes the mechanism of action of the prospective DMOADs on cartilage, although they may also structurally modify subchondral bone.

**Calcitonin**

Calcitonin is responsible for regulating calcium homeostasis and promotes osteoblastic bone formation. It inhibits bone resorption by binding to calcitonin receptors on osteoclasts. Calcitonin is indicated for the prevention of osteoporosis in postmenopausal women. It can be administered orally, intranasally, or subcutaneously. Its inhibition of subchondral bone turnover may be chondroprotective and, therefore, it may in-
Increased subchondral bone turnover in OA is integral to the pathogenic process of OA, and may be associated with pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), which can promote cartilage degradation and pain in OA.44 Nitric oxide—along with its metabolites—induces cartilage degradation and cytotoxic tissue damage via inhibition of proteoglycan and collagen synthesis, apoptosis of chondrocytes, and activation of matrix metalloproteinases (MMPs).

Initially, a phase 2 study of risedronate reported promising findings with a trend toward inhibition of JSN in knee OA. However, a subsequent phase 3 study of risedronate in knee OA reported no significant change in JSN or symptom severity.22 As yet, no study has accounted for the heterogeneity of the OA population regarding subchondral bone abnormalities when selecting patients. The insensitivity to change of conventional radiography used as an outcome measure (vide supra) for structural change suggests that the above-mentioned studies were significantly underpowered to show a response.23 Some potentially beneficial effects have nonetheless been observed. A reduction in biomarkers of cartilage degradation at 6 months of therapy was noted, along with slower knee OA progression.34

Zoledronic acid is a long-acting bisphosphonate that is licensed for postmenopausal osteoporosis. Along with other bisphosphonates, zoledronic acid has demonstrated chondroprotective effects in animal models of OA in conjunction with its impact on subchondral bone. In a 1-year randomized placebo controlled trial of zoledronic acid in patients with knee OA, zoledronic acid demonstrated a reduction in bone marrow edema (a marker associated with structural disease progression) and knee pain.36 As it improves symptoms and a marker of structural disease progression at the same time, zoledronic acid represents an important prospective DMOAD.

**Strontium ranelate**

Strontium ranelate is a drug used in the treatment of osteoporosis with antiresorptive and anabolic effects on the subchondral bone. Strontium ranelate influences bone remodeling through calcium-sensing receptors on osteoclasts and osteoblasts in subchondral bone and by an antiresorptive action via inhibition of osteoclastogenesis.37 In vitro studies suggest that strontium ranelate has anabolic effects on cartilage by directly promoting the formation of human cartilage matrix.38 In studies of human osteoporosis, strontium ranelate reduces cartilage degradation markers and inhibits clinical symptoms and radiographic features of spinal OA, indicating its potential as a DMOAD.39 A double-blind, placebo-controlled, randomized, international 3-year study of knee OA demonstrated a chondroprotective effect and symptomatic improvement in WOMAC (Western Ontario and McMaster Universities) index scoring.40

**Bone morphogenetic protein**

Human bone morphogenetic protein-7 (BMP-7)—also known as osteogenic protein-1 (OP-1)—is a transforming growth factor with a broad range of effects on a variety of cells, including cartilage. It signals through transmembrane serine-threonine kinase receptors, and is involved in cartilage homeostasis and repair via antiresorptive and anabolic properties.41 In animal models, BMP-7 demonstrated reparative effects on cartilage lesions.42 Human chondrocytes also promote cartilage formation in response to BMP-7 treatment.43 Clinical trials investigating the efficacy of BMP-7 in human knee OA have commenced.

**Inducible nitric oxide synthase**

Nitric oxide is considered to play a pathogenic role in cartilage degradation and pain in OA.44 Nitric oxide—along with its metabolites—induces cartilage degradation and cytotoxic tissue damage via inhibition of proteoglycan and collagen synthesis, apoptosis of chondrocytes, and activation of matrix metalloproteinases (MMPs).

### Table 1. Prospective disease-modifying osteoarthritis drugs (DMOADs) and their mechanisms of action on cartilage.

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<tr>
<th>Mechanism of action</th>
<th>Prospective DMOAD</th>
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<td>Anticatabolic</td>
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<td><strong>Systemic therapy</strong></td>
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<td>Strontium ranelate</td>
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<td>Aggrecanase inhibitors</td>
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<td>Doxycycline</td>
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<td>Cathepsin K inhibitors</td>
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<td>Anti-IL-1β</td>
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**Bisphosphonates**

Bisphosphonates are frequently used for treating conditions with osteoclastic bone resorption, especially osteoporosis. Increased subchondral bone turnover in OA is integral to the pathogenic process of OA, and may be associated with progressive cartilage loss.29 This disease-specific pathogenic process can be targeted using antiresorptive agents such as bisphosphonates, which hinder the bone remodeling process and could be chondroprotective. Animal models identified a beneficial effect of bisphosphonates in OA through their impact on subchondral bone, which includes inhibition of remodeling and osteophyte formation along with decreased vascular invasion of calcified cartilage.30
In animal models, selective inhibition of one isoform of nitric oxide synthase (iNOS) significantly reduces articular cartilage degradation and the number of osteophytes. There is also a significant reduction in the severity and incidence of OA in iNOS knock-out mice, indicating a potential role of iNOS in human OA. However, in a recent 2-year randomized, double-blind, placebo-controlled trial of an oral selective iNOS inhibitor, cindinustat, there was only a transient slowing of JSN in Kellgren-Lawrence grade 2 OA, which was not sustained at 2 years, and no significant evidence of inhibition of structural progression was seen in OA of greater radiographic severity.

**Matrix metalloproteinase inhibitors**

MMPs are collagenases that cleave type II collagen and result in loss of biomechanical integrity of normal human articular cartilage. This important pathogenic process in OA can be inhibited using MMP inhibitors. However, these MMP inhibitors have failed early clinical trials due to the frequent development of a painful musculoskeletal syndrome (MSS). This has been attributed to the broad spectrum of MMP inhibition. MMP-13 appears to be an important collagenase in human OA and specific inhibitors targeting it are in development. This more targeted approach will, hopefully, avoid MSS.

**Tissue inhibitors of metalloproteinases**

Aggrecan is an important protein found in articular cartilage that is degraded as part of the pathogenesis of OA. This process occurs as a result of the action of a variety of aggrecanases, including a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS). Endogenous inhibitors of MMPs include the tissue inhibitor of metalloproteinase TIMP-3, which can inhibit the action of these aggrecanases. Greater cartilage degradation was noted in TIMP-3 knockout mice compared with wild-type mice. Therefore, tissue inhibitors of metalloproteinases represent a prospective DMOAD target.

**Vitamin D**

Vitamin D is required for normal cartilage and bone metabolism. It regulates the expression of MMPs by chondrocytes. Vitamin D insufficiency is common and is associated with reduced osteoblast activity and reduced bone quality, which may explain its association with structural progression of OA. Several clinical trials are investigating the effect of vitamin D on structural disease progression.

**Fibroblast growth factor 18**

Fibroblast growth factor 18 (FGF-18) is involved in cartilage and bone development during skeletal maturation. In animal models, it has been shown to promote chondrogenesis, cartilage repair, and subchondral bone remodelling. It represents an important potential DMOAD and is currently undergoing phase 2 clinical trials examining changes in cartilage volume.

**Interleukin 1 inhibitors**

Interleukin 1 (IL-1) has been proposed to be involved in the degradation of articular hyaline cartilage based upon preclinical studies. Inhibition of the enzyme that activates the proinflammatory cytokine IL-1β, interleukin-1 beta-converting enzyme (ICE), has been achieved with a highly selective caspase-1 inhibitor called pralnacasan. In animal models, a reduction in joint damage was demonstrated. However, in human OA, monoclonal antibody IL-1 inhibitors have failed to demonstrate an improvement in symptoms.

**Neutraeuticals and supplements**

Glucosamine, an amino sugar, is a substrate for the formation of glycosaminoglycans, and chondroitin sulfate is a sulfated glycosaminoglycan. Glycosaminoglycans are important constituents of articular cartilage. The availability of these substrates may limit the formation of cartilage and therefore glucosamine and chondroitin were used in trials as prospective DMOADs. A recent meta-analysis of glucosamine and chondroitin concluded that there is no structural modifying effect of these agents based upon trials using JSN as a clinical end point.

Collagen hydrolysate is another dietary supplement. It is formed as a result of collagen hydrolysis and has only demonstrated small clinical improvement in OA. Phase 2/3 trials with collagen hydrolysate are yet to be published.

**Doxycycline**

Although there is no evidence to support an infectious etiology in OA, doxycycline has demonstrated potential as a DMOAD based on preclinical data. Possible mechanisms of action include inhibition of type XI cartilage degradation, inhibition of collagenase activity and a decrease in iNOS mRNA transcription. A randomized, placebo-controlled, double-blind trial of doxycycline of over 30 months that included 431 obese women with unilateral radiographic knee OA reported a small reduction in the rate of JSN in knees with established OA. Doxycycline is not currently recommended for the treatment of OA.

**Cathepsin K**

Cathepsin K, a cysteine proteinase, appears to play a role in the pathogenesis of OA. In preclinical models, cathepsin K inhibition reduced evidence of cartilage degradation. It, therefore, is a prospective DMOAD.

**Can we learn lessons from disease modification in rheumatoid arthritis?**

There may be some lessons to be learned from the management of rheumatoid arthritis, although the DMOADs that are used in the treatment of established OA are likely to differ from disease-modifying anti-rheumatic drugs (DMARDs) in some respects. DMARDs are typically used in a younger population where toxicity may be better tolerated and the absence of co-
morbidities and concurrent therapies to treat them permits the use of agents with greater potential toxicity. DMOADs for established OA will require excellent toxicity profiles in light of the greater prevalence of comorbidities and potential for drug interactions. However, DMOADs, like DMARDs, are likely to require chronic administration. OA affects a significantly greater proportion of the population than rheumatoid arthritis and, therefore, its treatment may represent a significant burden to health services. Ideally, DMOADs should be inexpensive, patient-administered, and require little or no monitoring in comparison with DMARDs such as tocolizumab and infliximab.

DMARDs are often prescribed in combination to improve the efficacy of treatment in terms of symptoms and structural disease progression. Similarly, DMOADs may also need to be prescribed in combination, particularly if a single joint tissue is targeted by the DMOAD. It is important to recognize that OA is a whole joint disease involving pathophysiological interactions between subchondral bone, cartilage, synovium, and ligaments and it is likely that an individual DMOAD will only target a single tissue, thereby increasing the need for combination therapy.

The cornerstone of DMARD therapy has been effective targeting of synovitis. While the synovium is only one of the tissues involved in OA pathogenesis, synovitis may contribute to disease progression. Therapies that modify synovitis could therefore potentially modify OA structural progression. Studies in this area are ongoing.

**Conclusion**

OA is the most common form of arthritis and is a chronic and progressive disease of the whole joint with only moderately effective treatment options currently available. There are a number of prospective targets for structural and symptomatic disease modification in patients with established OA, early OA, or at the time of acute joint injury, with a view to preventing structural progression, improving symptoms and function, and avoiding the need for total joint replacement. DMOADs are the highest unmet need in the field of OA and prospective DMOADs will need to demonstrate excellent safety profiles in view of their target population. However, DMOAD trials will require improved biomarkers and clinical end points to appropriately demonstrate the construct of OA structure modification.

**References**


Keywords: biomarker; cartilage; DMOAD; subchondral bone; structure
Les médicaments contre l’arthrose modifiant la maladie (DMOAD) :
que sont-ils et que peut-on en attendre ?

L’arthrose, forme la plus courante des arthropathies, représente un lourd fardeau pour les individus et les économies de la santé. Les traitements actuels reposent sur l’association d’interventions pharmacologiques et non pharmacologiques dans le but de réduire la douleur et d’améliorer la fonctionnalité. Ces traitements ne permettent pas d’éviter la détérioration structurale de l’articulation arthrosique : les besoins pour ce type de traitement sont donc immenses. La définition actuelle d’un « médicament contre l’arthrose modifiant la maladie » (DMOAD) est celle d’un produit qui inhibe la progression structurale de la maladie et qui, idéalement, améliore aussi les symptômes et/ou la fonctionnalité. À ce jour, aucun DMOAD n’a obtenu l’AMM, mais il existe de nombreux produits en cours de développement. Le développement des DMOAD est confronté à la mise en place de modèles animaux précliniques adéquats reproduisant l’arthrose humaine, aux limites du standard radiographique utilisé actuellement pour l’évaluation structurale de la maladie et au manque de stratification des patients par atteinte tissulaire ou phénotypique dans les études. De plus, il va probablement falloir utiliser les DMOAD dans les stades précoces de la maladie, avant l’établissement d’une pathologie irréversible, comme c’est fréquemment le cas au moment du diagnostic. Dans cette pathologie chronique d’une population vieillissante, les DMOAD vont vraisemblablement devoir être prescrits sur de longues périodes, ce qui exige d’excellentes données de sécurité pour leur utilisation chez une population sujette à de multiples comorbidités et donc, potentiellement, à de nombreuses interactions médicamenteuses. Dans cet article, nous passons brièvement en revue les questions relatives au développement des DMOAD, les DMOAD potentiels, les biomarqueurs utilisés en imagerie par résonance magnétique et les leçons tirées du traitement de la polyarthrite rhumatoïde.
This article aims to describe the economic weight of osteoarthritis (OA) in Europe based on published data and to underline the principal cost headings and their respective weights for patients and governments. This review suggests that OA has a significant economic effect not only on health care budgets, but also on patients, their employers, and their caregivers. The average total annual cost of OA per patient in Europe ranges from €1330 to €10,452. When considering only direct medical costs, the annual cost of OA ranged from €534 to €1,788. In active patients, the indirect costs were found to be much higher than the direct costs. European studies are, however, not directly comparable with each other because of differences in the approach taken, in patient characteristics, in health care systems, and in the calculation of productivity losses. Our review confirms the immense burden of OA in Europe, which is expected to rise substantially further in the future with demographic changes and increasing obesity. Developing effective and efficient treatment programs for OA is becoming increasingly important to reduce the clinical and economic consequences of this major public health problem worldwide.

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ities. In the United States, the annual medical care expenditures for OA were estimated at $185.5 billion (in 2007 dollars), of which $149.4 billion were insurer expenditures and $36.1 billion were paid directly by the patients. In Europe, some data has been published over the last few years on the economic impact of OA on individuals, including those in the workplace. The goal of this article is to review these publications so as to clarify the economic weight of OA in Europe based on available published data. Specific attention will be devoted to describing the principal cost headings (visits to health professionals, drugs, loss of productivity, etc.) and their respective weights for patients and governments.

Cost-of-illness evaluation

Burden-of-disease evaluation of OA aims to describe the impact of OA on society, including its impact on health care systems, patients, their caregivers, and their employers. Measuring the burden of disease can be very helpful in guiding the setting of health research priorities.11

The burden of OA can be measured with epidemiological parameters (incidence, prevalence) or with the impact of the disease on mortality, morbidity, quality of life, or health care costs. Cost-of-illness studies evaluate the direct and indirect health care costs of a particular disease over a period of time. This can be done using two different approaches: a prevalence-based approach and an incidence-based approach. While the incidence-based approach estimates the costs of new cases of the disease during the period of time considered, the prevalence-based approach includes the costs of all the patients affected by the disease. Prevalence-based studies are far more common and are more suitable for the estimation of the annual burden of a disease.12

The cost of a disease can be estimated using either a “top-down” or a “bottom-up” approach. The top-down approach examines the costs in an aggregated form (such as national indicators) while in the bottom-up approach, the overall cost is based on the costs for the individuals.11 Most cost-of-illness studies of OA in Europe have used the bottom-up method to estimate the economic burden of OA (see below).

The cost of a disease can be categorized into direct and indirect costs. Direct costs are those directly related to the disease, including, for example, visits to health care professionals, medical examinations, drug therapy, hospital admissions, and nonmedical costs. Indirect costs include productivity losses attributable to the disease resulting from absence from work and reduced effectiveness at work. These costs may be related to the patients themselves or to their caregivers.

Cost of osteoarthritis in Europe

A literature review was conducted using PubMed to find articles assessing the burden of OA in European countries between January 2000 and July 2012. The bibliographies of the papers included were also analyzed to search for additional references. Published studies on the economic cost of OA were found in Belgium, France, Germany, Italy, the Netherlands, and Spain. All of these studies, with the exception of the French study, used a bottom-up approach.

![Figure 1. Direct and indirect costs of osteoarthritis in Belgium.](image)

Based on a sample of 1811 active subjects with a mean age of 51 years. Total cost per year = €1330. Direct costs are represented in red and indirect costs in blue.


**Belgium**

In Belgium, the cost of OA was assessed in 2004 in a sample of 1811 active subjects employed by the Liège City Council (mean age, 51 years) who were followed prospectively for 6 months.13 The self-reported prevalence of OA was 34%. The burden of OA was measured comprehensively, taking into account the direct medical costs (consultations with health professionals and with alternative medicine professionals, the number and type of medical examinations, the number of hospital stays and emergency department consultations, and all drugs taken) and the indirect costs (the number of sick leave days, and the number of days off work taken by active subjects helping relatives or friends with OA).

The mean total direct and indirect costs were estimated at €44.50 and €66.30 per OA patient-month, respectively, which, when extrapolated to 1 year, came to €1330 per OA patient annually. The average distribution of costs is shown in
Figure 1. Consultations with health professionals, medical examinations, drugs, and hospital stays accounted for €23.70, €8.70, €6.70, and €4.90 per OA patient-month, respectively. Of all these direct costs, €29.10 (65%) was covered by the Belgian health care system and €15.40 (35%) was paid out of pocket by the patients. The average number of sick-leave days was 0.8 per OA patient-month, yielding—from the payer’s perspective—a cost of €64.50 per OA patient-month. The Belgian health care system covered 25.9% of all sick-leave payments, with employers covering the remaining 74.1%. In informal care was estimated to cost employers €1.80 per active subject-month, based on a mean of 0.02 days off work per active subject-month. Multiple regression analyses showed that age was a significant predictor of direct medical costs and that poorer quality of life was a major determinant of direct and indirect costs.

Italy

In Italy, the direct and indirect costs of knee OA were assessed retrospectively in a sample of 254 patients (mean age, 65 years) over a period of 12 months in 2000-2001. The cost per patient per year was estimated at €2170, of which 43% were direct costs—including medical (hospitalization, diagnosis, and therapies) and nonmedical costs (transport, temporary caregivers, and auxiliary devices)—and 57% were indirect costs (productivity losses and informal care).

The distribution of costs is shown in Figure 2. Hospitalization represented the largest medical cost, absorbing 25% of the direct resources (mean annual cost, €233). The annual cost of therapy was €136, of which 42% was spent on drugs and 58% on physiotherapy. Nonmedical costs (which represent 37% of the total costs) were mainly driven by temporary caregivers. In contrast with the study of Rabenda et al in Belgium,13 which only included active patients, the indirect costs were found to be mainly due to informal care provided by primary caregivers, which accounted for around 60% of the total indirect costs. The remaining indirect costs were due to loss of productivity (31%) and to other caregivers (9%). Sensitivity analyses revealed higher costs for patients with comorbidities and for women. Age was also shown to be a predictor of costs.

Netherlands

In the Netherlands, the productivity and medical costs of working patients with knee OA were recently assessed by Hermans et al.15 Loss of productivity and health care consumption were assessed by questionnaires in a sample of 117 knee OA patients participating in a randomized clinical trial investigating cost-effectiveness (mean age, 52 years). Interestingly, this study included the measurement of reduced work productivity while present at work in addition to loss of productivity resulting from absence from work.

The average total monthly knee OA–related costs were estimated at €871 per patient. The productivity costs accounted for 83% (€722) and the medical costs accounted for 17% (€149) of these costs. As observed in Figure 3, the medical costs were primarily driven by visits to primary (€62) and secondary care (€33), and by imaging (€40). Reduced productivity while present at work accounted for the majority (62%) of the productivity costs. The inclusion of loss of productivity while being present at work, which represented around 50%
of the total costs (€448 per patient-month), could explain the relatively high cost of OA found in this study. Logistic regression analyses reported that increased pain during activity and performing physically intensive work were significantly associated with loss of productivity.

**Spain**
The direct and indirect costs of osteoarthritis in Spain were estimated by Loza et al in 2007. Based on a sample of 1071 patients aged over 50 years (mean age, 71 years) with symptomatic and radiologic knee and/or hip OA who were seen at primary care centers in all provinces of Spain, data related to OA health resources utilization, patient and caregiver expenses, and time lost in the previous 6 months were collected in two separate interviews. The costs were divided into direct costs, including medical costs (professional time [all consultations], image, laboratory, and other tests, medications, and hospital admissions); and nonmedical costs (help at work and home, and self-care adaptive aids, devices, and assistive household equipment purchased), and indirect costs including compensation payments for lost productivity and housekeeping help costs if the patient was a homemaker.

![Figure 4. Direct and indirect costs of osteoarthritis in Spain.](image)

The average total annual cost of osteoarthritis was estimated at €1502 per patient (€2007). Direct costs accounted for 86% of the total cost, mostly due to home, work, and self-care help (29%), professional medical time (21%), and hospital admissions (13%) (Figure 4). Indirect costs represented only 14% of the total cost, with the largest component related to providing help for housewives at home. Assuming a prevalence of knee and hip OA of, respectively, 10% and 4% in Spain, the authors estimated the national cost of OA at €4.7 billion, which represents 0.5% of the gross national product (GNP) of Spain. Using regression models, the authors also found that higher costs were associated with comorbidity, poorer health status, and lower WOMAC score (Western Ontario and McMaster Universities Osteoarthritis index).

**France**
In France, the direct and indirect costs of osteoarthritis were estimated by Le Pen et al using the top-down approach with nationwide data from 2001 to 2003. The direct costs of osteoarthritis were estimated at 1.6 billion Euros (€2002), representing approximately 1.7% of the expenses of the French health insurance system. Hospitalization represented 50% of the direct expenses. The costs of medication and physicians were estimated at €574 million (34%) and €270 million (16%), respectively. A 156% increase in direct medical costs was reported compared with 1993, which was related to an increase in the number of OA patients (+54%). The authors mentioned that the cost per patient increased by only 2.5% per year.

**Germany**
In a recent article, Sabariego et al aimed to determine the direct medical costs in patients with osteoporosis, osteoarthritis, back pain, or fibromyalgia in Germany. The mean direct cost of OA was estimated at €1511 in a sample of 97 OA patients. Medication, outpatient physician visits, nonphysician services, and inpatient services accounted for €699, €357, €171, and €175, respectively.

**Other European countries**
For other European countries, no detailed estimations of the cost of OA have been published in any of the journals included in the database we searched. In the United Kingdom, however, the National Institute for Clinical Excellence (NICE) has reported that the burden of OA represents 1% of the GNP.

**Discussion**
This review suggests that OA represents a significant economic burden to patients and society in Europe. The annual cost of OA per patient ranges from €1330 to €10 452, depending on the country and the approach taken (Table). When considering only the direct medical costs, the annual cost of OA ranges from €534 to €1788. Drug therapies represent between 5.3% and 24.8% of the total direct medical costs, while hospitalizations and visits to health care professionals range from 15.2% to 39.6% and from 35.5% to 53.9%, respectively. Indirect costs range from €205 to €8664 per year, depending on patient characteristics and the mode of calculation of productivity losses. The direct and indirect costs of OA were shown to increase with patient age and with poorer quality of life in several studies.

Our review highlights the importance of indirect costs on the burden of OA. In particular, in studies assessing the burden of OA in active patients, indirect costs were found to be greater...
50% of the total cost of OA. To adequately estimate work efficiency were considerable, representing more than the Netherlands showed that the indirect costs related to reduced costs are especially high in OA. To adequately estimate the burden of OA, it is important to estimate not only the indirect costs due to time off from work but also to reduced work efficiency at work.

Cost variations were observed across the European studies. These studies are, however, not directly comparable because of differences in the approach taken, in patient characteristics, and in health care systems. Moreover, there are methodological differences in the calculation of productivity losses and no time adjustment was made for the costs. Despite such potential differences, the direct medical costs were very similar in Belgium, Italy, and Spain. The burden of OA is considerable, both from a societal and individual patient perspective. OA has a substantial effect not only on health care budgets but also on patients, their employers, and their caregivers. For example, in Belgium, the costs of OA in active patients are distributed among the employers (45%), the health care system (41%), and the patients themselves (14%). Therefore, in addition to pain and a poorer quality of life, patients living with OA may face significant personal expenses due to OA.

Our review confirms the great magnitude and economic impact of OA worldwide. Non-European countries have also reported a substantial burden of OA. For example, in the United States, the average direct cost of OA is approximately $2600 per year per person living with OA, while in Canada, the excess burden of OA was recently estimated at Can$. Cost-of-illness studies could be very useful in guiding health care priorities but there are limitations to their use for health care decision-making and they do not necessarily lead to more efficient health care systems. Cost-effectiveness analyses are potentially more interesting in order to assign health care resources more efficiently. By comparing the costs and effects of health interventions, health economic evaluation is a powerful tool for decision makers. However, current economic analyses in OA are limited and mainly pragmatic studies. Providing high-quality economic evaluations in OA would be of major importance to help decision makers make rational decisions and efficiently allocate health care resources dedicated to OA.

In summary, this review illustrates the immense burden of OA to patients and society in Europe. Developing adequate treatment programs for OA is becoming increasingly important to reduce the clinical and economic consequences of this major public health problem worldwide. Establishing the most effective treatments and determining the best use of resources should also become a priority in this area.

**References**

Keywords: burden, cost-of-illness, direct cost, economic, indirect cost, osteoarthritis

**LE POIDS ÉCONOMIQUE DE L’ARTHROSE EN EUROPE**

Cet article décrit, à l’aide de données publiées, le poids économique de l’arthrose en Europe et souligne les principaux coûts et leur poids respectif pour les patients et les gouvernements. Il montre que l’arthrose entraîne des conséquences économiques significatives non seulement sur les budgets de soins de santé mais aussi sur les patients, leurs employeurs et leurs soignants. Le coût annuel total moyen de l’arthrose par patient en Europe varie de 1 330 € à 10 452 €. Si l’on ne prend en compte que les coûts médicaux directs, le coût annuel de l’arthrose varie de 534 € à 1 788 €. Chez les patients actifs, les coûts indirects sont beaucoup plus élevés que les coûts directs. Les études européennes ne sont cependant pas directement comparables les unes avec les autres car les approches, les caractéristiques du patient, les systèmes de soins et le calcul des pertes de productivité diffèrent. Notre article confirme l’immense fardeau de l’arthrose en Europe, qui augmentera de façon importante dans le futur, avec les changements démographiques et l’augmentation de l’obésité. Il devient donc crucial de développer des programmes de traitement efficaces pour l’arthrose, afin de réduire les conséquences cliniques et économiques de ce problème majeur de santé publique dans le monde entier.
THE QUESTION

Although the development of secondary osteoarthritis can readily be pinpointed, the boundary between age-associated changes in articular cartilage and the pathogenetic changes related to primary osteoarthritis is not so easy to define. Changes in cartilage with age are likely universal, but development of osteoarthritis is not. This article will discuss the way to differentiate these two fates of the joint.

Can normal age-related changes in cartilage be distinguished from early osteoarthritic changes?

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Currently, osteoarthritis (OA) is the most common of all the musculoskeletal diseases, and this relates to the general increase in life expectancy and the accumulation of risk factors. The main symptom of OA and immediate reason for seeking medical care is pain, and this remains a permanent symptom over time. Despite traditional use of analgesic and anti-inflammatory drugs, most patients with OA continue to experience pain.

There are many reasons for the occurrence of pain in OA and many factors determining its severity. The proportion of patients with so-called "painful" or overtly symptomatic knee OA increases with age and reaches almost 80% in the oldest age group. Moreover, the individual perception of pain by each patient cannot be ignored, and may depend not only on changes in the joint, but also on the emotional and social status of the patient.

The source of pain in OA can be almost any structure of the joint: the synovial membrane, bone, or soft tissues. Mechanisms of pain perception may include activation and local release of pro-inflammatory mediators, such as prostaglandins and cytokines. Clinically, however, there is often a disparity between the degree of pain perception and the extent of destructive changes in the joint. A study with functional magnetic resonance imaging revealed that numerous areas in the brain are involved in the occurrence of pain in OA. This study demonstrated that perception of pain in OA is a complex mechanism involving local factors and the activation of central pain pathways.

On the other hand, articular cartilage has no innervation and cannot be a direct cause of pain, but the reduction in its thickness and volume with OA results in a higher load on the subchondral bone within the weight-bearing areas of the joint. Remodeling processes, which take place in these areas, lead to the development of osteosclerosis, osteophytes, and microfractures, and eventually to an increase in the stiffness of subchondral bone that can cause significant syndromic pain. Another cause of pain is the formation of foci of bone marrow edema and an increase in the intramedullary pressure.

In recent years, evidence has accumulated about the role of subchondral bone in the development of OA. Subchondral bone has been found to be able to produce a large number of proinflammatory cytokines and growth factors. Changes in its microarchitecture can influence the intensity of pain, and the bone mineral density value in subchondral areas of the tibia can be considered as a predictor of OA progression. All of this demonstrates the importance of investigating pain in OA, especially given the available information that pain can affect disease prognosis. As was described in the National Health and Nutrition Examination Survey (NHANES)–1 and by Mazzuca and colleagues, the initial level of pain in the knee joint in OA is a risk factor for the development of functional impairment and radiological progression in the future.

References
The etiology of osteoarthritis (OA) is not fully understood, but there are known to be several predisposing risk factors for the condition. These include obesity, injuries to the joints, and—most importantly—old age. The prevalence and incidence of OA increases with age. However, although epidemiological studies seem to indicate that primary OA and aging are interrelated, aging does not directly cause OA. Age-related changes in the musculoskeletal system may contribute to the development of OA by making the joints more susceptible to the effects of other OA risk factors. Several novel aging theories such as progressive apoptotic cell loss, mitochondrial degeneration, and cell senescence have been proposed to account for the cartilage degeneration in OA.

The pathogenetic changes in primary, and especially early, OA are difficult to distinguish clinically from normal aging, but there are some differences discernible between these two fates of the joint. The current research in this area focuses on articular cartilage.

Age-related changes in cartilage

Articular cartilage undergoes significant structural and mechanical changes with age. Articular cartilage collagen and proteoglycan metabolism are relatively active during growth and adolescence, but in adult individuals, the metabolism within cartilage is more sluggish. There is evidence of an increasing prevalence of articular surface fibrillation with age, and cartilage also thins with age, suggesting a loss of the cartilage matrix.

This might be due to the fact that chondrocytes become less responsive to the proliferative and anabolic effects of growth factors with increasing age. Aggrecan, the major cartilage proteoglycan, decreases in molecular size and content, and this would be expected to reduce cartilage stiffness and hydration. There is no major change in the content of total collagen and pyridinoline during aging, but there is a marked increase in the formation of advanced glycation end products, including pentosidine crosslinks, making the cartilage more brittle.

At the molecular level, OA is viewed as being a metabolically active process, including both cartilage destruction and repair. This equilibrium is regulated by the complex interplay between anabolic growth factors (especially TGFβ and IGF-1) and catabolic proinflammatory cytokines (especially IL-1 and TNFα). In a normal joint, these mediators are present at low levels to maintain the homeostasis of cartilage, but in OA, these processes become imbalanced, with the increased proteolytic degradation being mediated by matrix metalloproteinases, ie, collagenases and stromelysins.

Early diagnosis of osteoarthritis

The traditional diagnostic techniques, plain X-ray imaging or arthroscopic examination, can only detect late and major tissue changes in OA and are incapable of differentiating early cartilage OA changes from age-associated changes. However, early diagnosis would be highly advantageous as initial OA changes may still be reversible. Recent developments in quantitative imaging techniques, including magnetic resonance imaging and ultrasound methods, as well as more sensitive biomarkers, mean that diagnostic evaluation of cartilage in early OA may in the future become reality.

Cartilage in osteoarthritis

OA is characterized by a deterioration and progressive loss of articular cartilage, and it manifests clinically with pain that does not occur in normal aged cartilage. In experimental models of OA, some of the first detectable abnormalities that can be observed even before there is any deterioration visible on the cartilage surface include a decrease in the superficial proteoglycan concentration, increased water content, and the separation and disorganization of the superficial collagen fibrils. In early OA, the synthesis of both type II collagen and proteoglycans is increased. Advanced OA with fibrosis is accompanied by a net loss and damage to type II collagen fibrils, as well as a loss of proteoglycans. The loss of proteoglycans and collagen results in diminished cartilage stiffness.

References
The short answer is yes. However, interest and a degree of controversy derive from the techniques that are available to discriminate between the two and consideration of whether osteoarthritis (OA) is a disease restricted to cartilage alone or should more correctly be considered a disease of the whole joint.

The main techniques used to investigate cartilage include imaging, histology, and gene expression profiling. Clinically, the most useful test would be one that is noninvasive and readily available. Unfortunately, plain radiographs usually provide no direct visualization of cartilage, unless chondrocalcinosis is present, and the indirect evidence is limited by difficulties in interpreting joint space, which is affected by positioning, and the variable interposition of other low-density tissues such as menisci. High-resolution musculoskeletal ultrasound and magnetic resonance imaging can directly visualize cartilage, but there is a lack of true population data on age-related changes, even with magnetic resonance imaging. Large studies, for example Osteoarthritis Initiative, sponsored by the National Institutes of Health in the United States,¹ have focused on a single joint (the knee) and used convenience sampling.

Histological techniques include macroscopic examination of cartilage sections for thinning and fibrillation and microscopic examination with stains for proteoglycans (such as Safranin O). While grading systems for cartilage are discriminating for advanced disease, early OA changes may be difficult to discriminate from age-related change using grading systems for cartilage alone.² Three other approaches to discriminate early OA changes are: microscopic examination of the whole joint, measurement of specific enzymes upregulated in OA, and gene expression profiling. Pathological changes around the joint in early OA include synovitis and ligament/enthesis and subchondral bone abnormalities: the importance of these changes relates to their association with pain, which in clinical studies has been of stronger importance than early joint space narrowing (although advanced disease has a very strong relationship with radiographic change,³ in contrast to earlier assertions). Specific enzymes, such as matriptase, are upregulated in OA cartilage,⁴ which suggests potential relevance as a target for treatment.

However, probably the most definitive current technique for distinguishing OA from age-related change alone in cartilage is gene expression profiling. A recent study by Loeser et al⁵ has shown that there are quite different profiles in young versus aged mice, with 493 genes showing differential expression and an age-related decrease in matrix gene expression and increase in immune and defense response gene expression. Thus, there is a characteristic aging gene profile signature in mice. Replication in humans will provide us with an invasive tool for discriminating age-related change: arguably a controversial answer to the controversial question.

A growing appreciation of OA as a disease of the whole joint suggests that a narrow focus on cartilage alone is, however, probably counterproductive. Ongoing longitudinal studies will allow us to define which changes in and around the joint are associated with progression and response to treatment. We should increasingly use these predictors and regard cartilage changes as just one of several key outcomes of OA.

References
Can age-related cartilage changes be distinguished from early OA changes?

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Controversial question

Currently, it is not possible to give an exact answer to this question. In order to begin to answer the question, one must first elucidate whether or not aging of the cartilage is the same process as cartilage degradation.

As the role of mitochondria is known in degenerative diseases, a study was conducted to investigate mitochondrial function in healthy chondrocytes and osteoarthritic chondrocytes, as well as age-related changes in mitochondria. The study showed that mitochondrial mass was increased in osteoarthritic chondrocytes, but no correlation was found between mitochondrial function and age in normal and osteoarthritic chondrocytes. This result suggests that cartilage aging and cartilage degradation are two separate processes.

In another study, the matrix homeostasis of a healthy human ankle was evaluated. Type I collagen synthesis and denaturation were found to be associated with the pericellular matrix, and the type II collagen (CII) and proteoglycan content in the matrix were determined as remaining constant throughout life. Age had an important effect on the denaturation of CII, which decreased as age increased, relative to collagenase-mediated cleavage. These observations suggest that cartilage aging and the osteoarthritic process are two separate processes, since the aging of the ankle cartilage bore no resemblance to the molecular degenerative changes of osteoarthritis. Thus, a clear difference emerges between aging and osteoarthritis.

On the basis of the two aforementioned studies, new investigatory molecular studies could in the future be used routinely to help differentiate the early stage of osteoarthritis from cartilage aging. Currently, however, the results of studies such as these are not completely clear and remain to be clarified.

Additionally, contrary to the aforementioned results, aging is one of the most important risk factors in the development of osteoarthritis, and more than 50% of the population over the age of 60 years have osteoarthritic joints. Because osteoarthritis is a multifactorial disease and age is the major (but not only) risk factor, it is difficult to determine whether cartilage degradation and cartilage aging are different processes.

In an experimental study, the accumulation of advanced glycation end products (AGEs) was investigated in relation to osteoarthritis. AGEs adversely affect the formation of cartilage, lead to the formation of osteoarthritis, and increase with aging. In this study, the accumulation of AGEs was found to cause a tendency to develop osteoarthritis. The results showed that higher AGE levels in the cartilage increased the severity of osteoarthritis, and they provided the first in vivo molecular evidence to demonstrate the role of aging in the development of osteoarthritis.

With the development of microarray technology, studies have emerged suggesting that gene expression analysis of subchondral bone can be conducted in early experimental osteoarthritis and can be used in its diagnosis and treatment. However, it is currently impossible to obtain suitable subchondral bone and cartilage samples from humans and animals in order to study the beginning and early stages of osteoarthritis. Another study indicated that by measuring certain biomarkers of bone, cartilage, and synovial metabolism (sC2C, uCTX-II, sCPII, uNTx, and sHA), changes in cartilage matrix and early structural changes in cartilage could be identified.

This and many similar studies show that biomarkers may be important indicators of early-stage osteoarthritis. With such biomarkers, it could be possible to differentiate early osteoarthritis from cartilage aging.

To date, studies have not been able to clearly reveal the distinction between osteoarthritis and cartilage aging. It is therefore difficult to distinguish primary osteoarthritis in its early stages from cartilage aging, hence the need for further studies in this area.

References
Can age-related cartilage changes be distinguished from early OA changes?

Osteoarthritis (OA) is a disease of the joint affecting all joint tissues. Similarly, joint aging is systemic. Age is the most prominent risk factor for OA, and although the relationship between aging and OA is well known, its mechanisms are not fully understood.

Joint changes that are both intrinsic and extrinsic (sarcopenia, altered bone remodeling, reduced proprioception) contribute to OA development. The concept that aging contributes to, but does not directly cause OA, is consistent with the multifactorial nature of the condition and the joints most commonly affected. OA normally develops after long periods of exposure to risk factors such as obesity, joint trauma, joint malalignment, or abnormal shape and leg length inequality. Age-related changes occur in the joint tissues of all individuals, most notably in articular cartilage. However, symptomatic, radiographic, macroscopic, or microscopic signs of OA do not manifest in all individuals, even at an advanced age. This suggests that aging does not necessarily cause OA, rather age-related changes provide a basis upon which OA can develop.

Individuals with OA risk factors may undergo an accelerated rate of change similar to that associated with aging, consistent with the concept that aging results from an imbalance between stressors causing damage and mechanisms that repair or protect against damage.

In both aging and OA, changes occur in the total amount and composition of articular cartilage extracellular matrix, which also undergoes proteolysis and other modifications. The superficial zone is where the earliest age-related changes occur in human articular cartilage. In OA, increased proteolytic activity in cartilage and synovial fluid causes cartilage matrix changes and increased degradation of collagen molecules. There is also a decrease in fixed charge density due to degradation and loss of aggrecan.

Normal aging involves a marked increase in the formation of advanced glycation end products, including pentosidine cross-links. The resultant increased crosslinking of collagen molecules can alter the biomechanical properties of cartilage, resulting in increased stiffness and susceptibility to fatigue.

A highly prevalent change in aging cartilage is deposition of calcium-containing crystals due to increased pyrophosphate production by chondrocytes. Calcium crystals may stimulate chondrocyte production of inflammatory mediators and extracellular matrix-degrading enzymes, contributing to the onset and progression of OA, and may play a role in erosive OA, a more destructive form of OA most commonly seen in the distal interphalangeal joints in elderly women.

Age-associated cellular changes in articular cartilage include cell depletion and impaired responses to extracellular stimuli resulting in abnormal gene expression and cell differentiation. In full-thickness cartilage, cell density decreases with aging. In OA-affected cartilage, chondrocyte proliferation in the form of “cell clusters” or “cloning” has been observed in areas of fibrillation. Cells in these clusters express progenitor cell markers and a wide spectrum of proteins associated with abnormal chondrocyte activation and differentiation. This represents a tissue repair response of progenitor cells. The activation pattern of the cluster cells also underscores the notion that aging does not uniformly affect all cells in cartilage and that certain cell subsets in aging and OA-affected cartilage are capable of proliferation and activation.

With increasing age, chondrocytes become less responsive to the proliferative and anabolic effects of growth factors, which may contribute to an imbalance between anabolic and catabolic activity. Altered cell signaling in response to growth factors may also account for the reduced anabolic response with age.

Conceptually, age-related pathologies originate from limitations in the maintenance and repair mechanisms of DNA, anomalies in the antioxidant mechanisms that contribute to the detoxification of reactive oxygen species, or abnormalities in mechanisms for removal of abnormal proteins and organelles. A clear distinction between aging and OA has not always been provided, so that it can be difficult to differentiate primary age-related changes from those that are part of the OA process.
Osteoarthritis (OA) is a slow-developing disease of the diarthrodial joints associated with progressive cartilage damage, soft tissue and subchondral bone changes, bony osteophytes, and joint inflammation. OA is most common in the hands, causing significant pain and functional loss, but involvement of the knees or hips is usually more disabling. Aging is the most important risk factor, followed by obesity, previous joint injury, female sex, and genetic disposition. Two fundamental mechanisms lead to OA: normal load on abnormal cartilage (primary OA) or abnormal load on normal cartilage (secondary OA). Although cartilage aging is universal, OA is not found in all elderly people; a proportion of them are free of symptomatic and radiographic OA, indicating the presence of additional risk and/or protective factors.

There are several theories explaining the pathogenesis of primary OA. The oldest theory, wear and tear of the cartilage matrix, emphasizes the effect of mechanical load over a lifetime. The extracellular matrix theory links OA to intrinsic changes in proteoglycans, the collagen network, and chondrocyte biology that are caused by advanced glycation end products and oxidative stress. The apoptotic theory views OA as the result of chondrocyte apoptosis or other types of cell death. The mitochondrial theory emphasizes the role of mitochondrial DNA damage, which may be advanced by inflammatory cytokines, contributing to chondrocyte energy failure and death. A recent theory on cell senescence describes OA as the increasing inability of the chondrocytes to keep up with mechanical or inflammatory attacks leading to failure in maintaining cartilage integrity.

The causes of cell aging remain unclear, but it is increasingly accepted that there are a limited number of cell replication cycles, culminating in replicative senescence. Replication is limited by telomere exhaustion. Telomeres are eroded by each division cycle, eventually down to the minimum length for DNA replication, resulting in cycle arrest.

In adults, subchondral bone isolates cartilage from the vascular system, resulting in no influx of progenitor cells into cartilage. Chondrocytes are postmitotic, with little or no cell turnover, and are among the oldest cells in the body. They accumulate age-related changes and are also unable to move from damaged regions due to the constraint of the extracellular matrix. Aside from aging, repeated injuries (joint instability) increase the requirements for replication and damage repair and thus contribute to the exhaustion of mitotic potential. As a result of the specific local environment, oxidatively damaged molecules can accumulate in chondrocytes, leading to a decreased ability to maintain matrix synthesis and homeostasis. Chondrocyte senescence reduces the ability to respond to growth factor stimulation, contributing to an imbalance in cartilage formation and degradation, as well as decreased chondrocyte anabolic activity. Furthermore, senescence-associated secretory phenotype (SASP) may negatively affect the local environment. Cells exhibiting SASP produce proinflammatory cytokines and matrix metalloproteinases very similar to those in OA. Another cell senescence factor, high-mobility group box protein 2, regulates gene transcription and decline in the superficial zone of aging chondrocytes and is associated with increased chondrocyte death in OA models.

Current findings support the view that cartilage aging usually occurs before overt primary OA. In many cases, it is impossible to distinguish the senescent chondrocyte from the osteoarthritic chondrocyte because cell senescence is the number one precondition for OA. There is some evidence of increased chondrocyte proliferation during the development of OA, and chondrocyte death has also been observed, with reduced numbers particularly in the superficial regions of cartilage. However, it is not clear if the cell damage and reactivity represent changes associated with the aging process, early OA, or a continuum from aging to OA.

A better understanding of the role of senescence biology in OA development may translate practically into the development of new strategies to delay the onset of chondrocyte senescence and prevent the development or progression of OA.

Further reading
Osteoarthritis (OA) is a common age-related disorder, often described as a chronic degenerative disease and thought by many to be an inevitable consequence of growing old. Epidemiological studies show that age remains the most prominent risk factor for the initiation and progression of primary OA in susceptible joints. The prevalence of OA increases with age: radiographic surveys of multiple joints (hands, spine, hips, and knees) reveal the presence of OA in at least one joint in over 80% of older adults. However, not all older adults with symptoms of joint pain have radiographic evidence of OA in the painful joint, and only about half of people with radiographic OA experience significant symptoms. Moreover, it is well-known that not all older adults develop OA and not all joints in the body are affected to the same degree. It is also well-known that radiographic OA changes, particularly osteophytes, are common in the aged population, but symptoms of joint pain are frequently independent of radiographic severity. Consequently, due to the discrepancies between osteoarthritic pain and radiographic evidence of OA, most current epidemiological studies define OA through a combination of clinical and radiographic criteria.

The current concept is that OA is a disease of the “whole joint,” which involves a complex series of molecular changes at the cell, matrix, and tissue levels and complex interactions between the tissues that make up the joint. Aging is the major risk factor, and it contributes to, but does not directly cause OA. This is consistent with the multifactorial nature of the condition and the differing joints most commonly affected. Besides age, the common risk factors for OA include obesity, previous joint injury, genetics, and anatomical factors including joint alignment. These risk factors appear to interact with age to determine which joints are affected by OA and how severe the condition will be. Thus, there are important differences between an aged joint and one with OA. Age-related mechanical stress on joint cartilage (arising from a number of factors, including altered gait, muscle weakness, degeneration of ligaments, changes in proprioception, and changes in body weight), and changes within the joint (including cell and matrix changes in joint tissues, thickening of the subchondral bone, variable degrees of synovial inflammation, loss of meniscal tissue, and hypertrophy of the joint capsule contributing to joint enlargement) contribute to the development of OA when other OA risk factors are also present. The pathological changes noted in the other joint tissues also contribute to the loss of normal joint function, and because, unlike cartilage, they contain pain fibers, these tissues are responsible for the pain experienced by people with OA.

Thus, it is very important to question how to distinguish normal age-related changes in cartilage that do not progress to OA from early changes that reliably do progress to OA. In this regard, magnetic resonance imaging (MRI) studies have shown promising results. New methodological approaches for quantitative assessment have been introduced, and an MRI-based definition of OA has been suggested. A recent study using MRI methods sensitive to cartilage matrix composition demonstrated that subjects at risk for OA have both higher and more heterogeneous cartilage T2 values than controls, and that T2 parameters are associated with morphologic degeneration. One could speculate that the development of these kinds of techniques could help to distinguish age-related changes in cartilage that predispose patients to OA from those that do not. More information is needed to better understand how aging changes in the bone, meniscus, and ligaments contribute to the development of OA.

References
Articular cartilage is a unique tissue from the perspective of aging, in that chondrocytes and the majority of the extracellular matrix proteins experience little turnover, thus resulting in a tissue that must withstand years of use and can also accumulate years of aging-associated changes. It has been known for a very long time that aging is the most prominent risk factor for the initiation and progression of osteoarthritis. This might be related to continuous mechanical wear and tear and/or time/age-related modifications of cartilage matrix components. In addition, a mere loss of viable cells over time due to apoptosis or any other mechanism might contribute. More recent evidence, however, supports the notion that stressful conditions for the cells might promote chondrocyte senescence and be particularly important in the progression of the osteoarthritic disease process.1

In animal models, aging predisposes articular cartilage to changes in viable cell density and to expression of specific pro-apoptotic genes. Also, fetal and young (but still skeletally mature) bovine chondrocytes behave similarly, while aged chondrocytes display diminished proliferation, slightly reduced proteoglycan accumulation, and significantly less collagen accumulation per cell compared with the younger cells. Histological observations and mechanical properties support these findings, and a particularly significant reduction in the tensile stiffness produced by aged chondrocytes compared with younger cells has been observed.2

In humans, chondrocytes from normal but aged subjects display biochemical properties closer to osteoarthritic-derived cartilage than to normal young cartilage, as indicated by cell morphology, cell proliferation rate, and patterns of protein secretion (in particular stromelysin-1 and interstitial collagenase).3 During aging, nonenzymatic glycation results in the accumulation of advanced glycation end products (AGEs) in cartilage collagen. The highest AGE levels are found in tissues with slow turnover, such as cartilage. AGEs exert their effects by adversely affecting the biomechanical, biochemical, and cellular characteristics of the tissue, as well as by modulating tissue turnover.

This ultimately increases cartilage stiffness and brittleness, increases chondrocyte-mediated proteoglycan degradation, reduces resistance to matrix metalloproteinase-mediated degradation, and decreases proteoglycan synthesis by chondrocytes. Articular cartilage becomes more prone to damage and development of osteoarthritis.4

In addition, an age-associated reduction in growth factor signaling and an increase in oxidative stress may also play an important role in the age-osteoarthritis connection.5

Although different studies have shown that age is inversely associated with cartilage volume, cartilage turnover, and aggrecan expression in healthy individuals, the exact differentiation between aged cartilage and early osteoarthritic cartilage seems difficult, and age-related changes leading to failure of human articular cartilage to resist damage are considered to be OA.6

References
Aging is the main risk factor for primary osteoarthritis (OA) and OA is the disease most strongly correlated with aging. Both in humans and other animals, OA development seems to be not rigorously time-dependent, but to hold pace with the aging process. Despite older age being the greatest risk factor for OA, OA is not an unavoidable consequence of growing old. Moreover, radiographic changes indicative of OA—mainly osteophytes—are frequent in the aged population, but symptoms of joint pain may not correlate with the severity of radiographic findings in many older subjects.

OA is a degenerative disease characterized by structural changes to joint tissues that include synovial inflammation, catabolic destruction of articular cartilage, alterations in subchondral bone, and decreasing muscle strength.

This article will only address differences between cartilage changes caused by OA and those caused by aging. The effects of aging involve the whole articular cartilage. Major extracellular matrix changes comprise reduced cartilage thickness, proteolysis, advanced glycation, and calcification. Cellular changes consist of decreased cell density, cellular senescence with reduced chondrocyte survival, decreased mitotic and anabolic activity, anomalous cytokine excretion, and impaired cellular resistance.

One of the most pronounced age-related changes in chondrocytes is a senescent phenotype, which is caused mainly by the accumulation of reactive oxygen species (ROS) and advanced glycation end products. Senescent chondrocytes display an impaired ability to respond to many mechanical and inflammatory insults. Protein secretion is also altered in aging chondrocytes, as demonstrated by a decrease in anabolic activity and increased production of proinflammatory cytokines and matrix-degrading enzymes. The senescent secretory phenotype has some features in common with the OA chondrocyte phenotype, including increased production of cytokines and matrix metalloproteinases.

The age-related increase in ROS levels could play an important role in OA. The various inflammatory mediators that are increased in OA, including IL-1, IL-6, IL-8, TNF-α, and other cytokines, can all stimulate additional production of ROS. Excess ROS production can directly damage intracellular proteins and DNA, as well as the extracellular matrix, by stimulating matrix metalloproteinase production and activity, thus playing a significant role in stimulation of cartilage degradation in OA.

The extracellular and cellular changes in aging compound each other, leading to biomechanical dysfunction and tissue destruction. Some of these changes differ from those seen in OA, which is also characterized by cell activation with increased proliferation and gene expression. Disruption of the articular surface or superficial zone (SZ) seems to be a key triggering event for the chronic and progressive extracellular matrix degradation process leading to OA. The SZ contains the majority of mesenchymal stem cells in adult cartilage. The presence of stem cells endows the SZ with the capacity for self-renewal, which may be required to respond to mechanical stress. However, the SZ can be compromised by acute or chronic mechanical stress and by age-related cellular dysfunction. Once the SZ is disrupted, cartilage cells are activated, and through the production of matrix-degrading enzymes, lesions enlarge causing joint inflammation, pain, and dysfunction. Loss of cells (e.g., via apoptosis) is among the major changes that occur in the SZ due to aging and exposure to mechanical stress.

Cartilage degradation results in the production of fragments of extracellular matrix molecules. Some of these molecules may be detected in blood, serum, synovial fluid, and urine, and can act as useful biomarkers. The ability to detect biomarkers of cartilage degradation may enable clinicians to differentiate the appearance of subclinical OA from natural joint aging. Biomarkers indicating early phases of degeneration would be useful in detecting preradiographic OA changes. Proteomic techniques have the potential to improve our understanding of OA pathophysiology.
Osteoarthritis (OA) is the most frequent joint disease and an important cause of disability in the Western world. It involves all parts of articular joints and is characterized primarily by the progressive, irreversible loss of articular cartilage. Given that the incidence of osteoarthritic changes increases with age, the question of whether OA is a mere aging phenomenon or as with cardiovascular disorders, cancer, or neurodegenerative diseases, becomes more frequent during aging because of the cumulative effects of pathogenic factors (which in principle can affect individuals at any age), is a controversial, yet important, one.

One main reason for the difficulty in answering this question is that the processes that lead to and characterize normal cartilage aging remain largely unknown. While it is well accepted that the composition of the extracellular matrix changes with aging, aside from the loss of proteoglycans, disease-specific alterations in osteoarthritic cartilage are poorly characterized and understood. Also, OA most likely does not constitute a uniform disease, but rather an initially complex yet ultimately narrow path of how cartilage responds to different types of stress. In this context, it has been suggested that inflammation is a distinguishing factor between normal aging and OA. However, the role of inflammation as a trigger and accelerating force of osteoarthritic changes remains controversial, and while some recent data suggest a key role for inflammatory signals, the most recent studies have failed to demonstrate a key role for IL-1–mediated inflammation in murine models of OA. Of interest, several lines of evidence indicate that osteoarthritic changes are linked to the reexpression in chondrocytes of molecules and pathways that are characteristic of different stages of endochondral ossification during embryonic development.

Members of the syndecan family of transmembrane heparin sulfate proteoglycans, particularly syndecan-4, are prominent examples in this respect. We were able to show that syndecan-4, which is expressed prominently in hypertrophic chondrocytes of developing joints in the embryo, is reexpressed both in human OA and in animal models of the disease, and its concentration correlates with disease severity. Interestingly, the loss of syndecan-4 in genetically modified mice, as well as its inhibition by specific antibodies, was capable of preventing the development of OA-like changes. These data are also of interest because according to recent data, increased expression of syndecan-2 can compensate for the loss of syndecan-4 during embryogenesis but not during OA, due to differential regulation of these two syndecans. While the exact mechanisms are not fully understood, these data suggest that while the program appears to be similar, the triggers and mechanisms of cartilage remodeling during endochondral ossification and OA may be distinct.

Given that during endochondral ossification, deposition of basic calcium phosphate crystals is an important part of bone formation, calcification of articular cartilage during OA is another indication of similarities between both conditions. Our group found that the calcification of hyaline cartilage is a regular event in human OA and is strongly associated with the hypertrophic differentiation of chondrocytes. The mechanisms involved in pathological cartilage calcification during OA, and particularly the pathways that link chondrocyte differentiation to the calcification of the surrounding matrix, are not completely understood. However, changes in the synthesis and transport of inorganic pyrophosphate, as well as in extracellular pyrophosphate metabolism, have been found to be associated with this process.

Collectively, these data indicate that while mechanistically similar and part of a rather uniform program, the developmental processes that occur either during embryogenesis or during aging can be distinguished from the pathological changes seen in OA. Distinguishing factors appear to include the nature, strength, and duration of underlying stimuli.

References
Osteoarthritis (OA) is probably the most common chronic joint disorder. It is defined by focal lesions of the articular cartilage, a hypertrophic reaction in the subchondral bone, and new bone formation. OA is often considered a chronic degenerative disease, with degradation of articular cartilage attributed to wear and tear. Although aging is a known risk factor for OA, the condition is not a consequence of growing old, but involves a destructive chronic active inflammatory mechanism mediated by cells within the articular cartilage.

In OA, there is a change in the normal adult chondrocyte state characterized by cell proliferation, cluster formation, and increased production of matrix proteins and matrix-degrading enzymes. Chondrocytes in OA cartilage express cytokine and chemokine receptors, matrix metalloproteinases (MMPs), and other proteins that enhance or modulate inflammatory and catabolic responses. MMPs such as aggrecanases and collagenases are found in the osteoarthritic joint. In early OA, MMP-3 and ADMTS-5 degrade aggrecan. Next, collagenases degrade type II collagen and the collagen network. As the articular cartilage matrix proteins are degraded, fragments of matrix proteins such as fibronectin and small leucine-rich proteoglycans are produced, which can feed back and stimulate further matrix destruction. This early stage may reflect an effort by the hypertrophic chondrocytes to repair cartilage damage. As OA progresses, the proteoglycan level eventually drops very low, causing cartilage to soften and lose elasticity, thereby further compromising joint surface integrity.

Aging produces a gradual loss of cartilage matrix as well as a decrease in cartilage hydration and cellularity. Aging cartilage is characterized by an age-related loss in the ability of cells and tissues to maintain homeostasis. Normal aging chondrocytes are reduced in number, rarely divide, and exhibit no cellular proliferation or hypertrophic cells. They show shortened telomeres characteristic of cellular senescence. However, aging chondrocytes can exhibit a senescence secretory phenotype, characterized by increased production of cytokines, MMPs, and several growth factors. As a result, in the elderly, there is increased age-related cartilage catabolism. Besides these mechanisms, the chondrocyte anabolic response to growth factors decreases with age. Under such circumstances, the chondrocyte is unable to maintain cartilage homeostasis. Cell death has also been related to aging, and formation of advanced glycation end products (AGEs) increases with age. Modification of collagen by AGE formation results in increased crosslinking of collagen molecules affecting the biochemical properties of cartilage and making it more brittle. Moreover, there is an age-related increase in reactive oxygen species, and this may contribute to cell death and matrix degeneration.

There is no clear frontier between the features of articular cartilage in aging and OA, and both share some common characteristics. Senescent and osteoarthritic chondrocytes share a secretory phenotype. Cell death has been observed during the development of OA as well as in aging cartilage. Age-related loss of autophagy, a protective mechanism for normal chondrocytes that protects cells during the stress response, is associated with cell death and OA development. Age-related changes in cartilage matrix could also be important in contributing to the development of OA. The increased accumulation and expression of AGEs that occurs in aging chondrocytes is associated with enhanced sensitivity to cytokines and chemokines, which trigger expression of MMPs. The increased production of reactive oxygen species could also play an important role in OA.

The relationship between aging and OA is well known, but the mechanisms by which aging predisposes the joint to OA development are not fully understood. Age-related changes observed in cell and cartilage matrix may increase the susceptibility to OA, but they do not directly cause it in older adults. More information is needed to better understand how aging changes in the bone, meniscus, and ligaments contribute to the development of OA.

References
Osteoarthritis (OA) is considered a characteristic age-related disease. Its prevalence increases with age, affecting 30% to 50% of adults aged over 65 years. Although it is the greatest risk factor for OA, older age alone is not responsible for its development. Age, obesity, female sex, previous trauma (knee injury), and hand OA were reported as consistent risk factors for knee OA in people aged 50 years and older. Risk factors for OA such as obesity, genetics, anatomical abnormalities, and joint injury are well known, but how they interact with age to initiate and develop OA is still unclear. Recent advances in molecular biology are starting to clarify the connection between cellular aging changes and the propensity to develop OA.

Chondrocytes are the only cell type in articular cartilage, and they particularly suffer during aging. They are responsible for the synthesis and breakdown of the cartilaginous matrix and are driven by signals from growth factors, cytokines, and the matrix itself. The chondrocytes of older cartilage are the same cells present in the cartilage during youth. Chondrocytes rarely divide or die in normal adult articular cartilage, with the same cells remaining active for many years. Chondrocytes have a very long lifespan, but in older individuals they may express changes characteristic of cell senescence. Cell senescence found in chondrocytes is called stress-induced or “extrinsic” senescence, as opposed to replicative or “intrinsic” senescence. Stress-induced senescence can develop from stimuli including activated oncogenes, ultraviolet radiation, and chronic inflammation. Stress-induced senescence is associated with oxidative DNA damage, which results in telomere shortening (as in replicative senescence). Many age-related changes in chondrocytes, particularly oxidative DNA damage, may induce development of the senescence-associated secretory phenotype (SASP). This phenotype when expressed in chondrocytes may link the articular aging process with the development of OA. SASP is characterized by increased production of inflammatory mediators such as cytokines and matrix metalloproteinases, which may induce cartilaginous matrix degradation and joint impairment and may also be found in osteoarthritic cartilage. SASP expression in chondrocytes may be linked to the production of reactive oxygen species (ROS) by dysfunctional mitochondria, resulting in mitochondrial and nuclear DNA damage. Mitochondrial DNA damage can be observed in OA and is associated with increased matrix degradation and decreased matrix synthesis. ROS production may be induced by inflammatory cytokines such as IL-1β and TNF-α, and is also associated with mechanical injury to joints. An increase in ROS may contribute to chondrocyte death.

Thus, ROS, mitochondrial dysfunction, and DNA damage may be features of chondrocyte senescence associated with development of SASP and may lead to cartilage matrix impairment and development of OA.

Aged and osteoarthritic chondrocytes have a reduced ability to respond to transforming growth factor-β and insulin-like growth factor-1 (IGF-1) stimulation. This leads to a reduced capacity for matrix repair, and consequently, a degeneration of the articular cartilage. The decrease in chondrocyte responsiveness to IGF-1 is associated with increased ROS levels.

Autophagy is a mechanism used by the cell to degrade and recycle dysfunctional proteins. It is an important mechanism by which cells are protected against stress. Autophagy declines with age, and its loss has been associated with increased chondrocyte death. Recent studies in autophagy have attempted to clarify the possible role of this process in senescence and OA.

Thus, to answer the question, we must determine if and when the aging process results in the development of SASP. Senescent chondrocytes developing this phenotype are very similar to chondrocytes found in osteoarthritic joint tissues. In my opinion, development of this phenotype with its associated inflammatory cytokines, or lack of it, will determine how much we can distinguish between normal age-related changes in cartilage and early osteoarthritic changes.

**References**

The goal of this interview is to better understand the role of nonpharmacological treatments in osteoarthritis. A wide spectrum of treatment options is available, ranging from adaptation of activity levels, exercise, and physiotherapy, to intra-articular injections, surgical unloading of the degenerated joint compartment, and knee replacement. While the aim of all treatments is to improve symptoms, function, and therefore quality of life, each has its own advantages and disadvantages and is more suitable for certain specific phases of joint osteoarthritis. There is currently no agreement on the most effective management of osteoarthritis, and none of the available treatment options have been proven to produce better results over all others or have been clearly shown to have disease-modifying properties. In general, the optimal conservative management of knee osteoarthritis requires a combination of pharmacological and nonpharmacological treatment modalities. Among nonpharmacological treatments, a combination of different approaches is also recommended. Aside from considering the treatment to be applied, one must also consider that osteoarthritis is a chronic condition and that long-term disease management can be cumbersome. Thus, therapeutic education of patients with osteoarthritis is of major importance. Finally, prostheses produce a high percentage of good results but require adaptation to the activity level of the patient and also carry some important risks related to the surgical implant. Thus, when treating a patient affected by osteoarthritis, it is important to consider all the available options for improving the clinical condition of the patient and keep prosthetic replacement as a last option for when functional limitations and symptoms prove to be refractory to less invasive procedures.

Interview with E. Kon, Italy

When should nonpharmacological management of osteoarthritis be started?

The etiology of osteoarthritis (OA) is multifactorial. Age is the major independent risk factor for OA; however, aging and OA are interrelated, not interdependent. It is becoming apparent that age-related changes in the musculoskeletal system contribute to the development of OA by working in conjunction with other factors that are both intrinsic (eg, malalignment, overloading) and extrinsic (eg, genetics) to the joint. Regardless of the initial cause, once started, osteoarthritic alterations lead to progressive loss of hyaline cartilage, leading eventually to end-stage OA.
Thus, nonpharmacological OA management should be started even before the clinical onset of symptoms, with the aim of treating the predisposing factors. Early OA should be detected. Clinical recurrence of pain and discomfort of the knee and/or short periods of stiffness, in between long periods with very few clinical manifestations, should set the stage for performing additional investigations such as radiographs, ultrasound, magnetic resonance imaging (MRI), or arthroscopy.1

Malalignment, loss of meniscal tissue, cartilage defects, and joint instability or laxity should be evaluated, and treatment (including surgery if appropriate) should be discussed with the patient, taking into consideration their activity level and expectations as well as the risks of failure and complications associated with every procedure.

In addition to its preventative use in the early phase, nonpharmacological management should also always be considered when OA is clearly established. Of course, when considering treatment options, one should also always take into consideration the disease phase and the invasiveness of the procedure.

Nonpharmacological management is a broad definition, ranging from physiotherapy to knee replacement. While noninvasive treatments such as exercise and physical therapy should be started in the earlier phases, injective treatments should be considered for the management of patients after noninvasive procedures have failed. Prosthetic replacement, which is an irreversible procedure, should of course be reserved as a last option during the advanced and debilitating phases of OA refractory to other treatments.

What is the cornerstone of nonpharmacological treatment?

There is no cornerstone of nonpharmacological treatment. As previously underlined, this is a broad definition, ranging from adaptation of activity levels to exercise, from physiotherapy to intra-articular injections, from surgical unloading of the degenerated joint compartment to knee replacement, and so on.2,3,4 While all treatments are aimed at improving symptoms, function, and therefore quality of life, every treatment presents its own advantages and disadvantages and is more appropriate for specific phases of joint OA. One nonpharmacological approach that is probably indicated across different phases of articular degeneration with minimal contraindications is exercise.

International clinical guidelines recommend exercise as an effective approach in the management of knee OA. The aims of exercise in these patients are to reduce pain, improve physical function and health status, and prevent progression of the disease. While the optimal dosage (frequency, intensity, and duration) has not yet been determined, good results have been reported for different types of exercise.5 In general, physical activity is beneficial, rather than detrimental, to joint health, and an MRI study showed that moderate exercise may also improve the knee cartilage glycosaminoglycan content in patients at high risk of developing OA, but long-term effectiveness still needs to be clarified.6

As mentioned, injective treatments also play an important role in the management of OA, ranging from corticosteroids to viscosupplementation and also to more innovative biological procedures such as the use of blood derivatives to aid in the restoration of joint homeostasis and tissue regeneration.7

Moreover, although the degenerative OA environment is an obstacle to tissue regeneration, progress made in bioengineering and the development of new scaffolds seems to represent a promising solution that may help to avoid, or at least delay, the need for more sacrificing metal resurfacing procedures.8

How should cost, availability, or practicality of delivery be taken into account?

Cost, availability, and practicality of delivery should always be taken into account in the management of OA patients, especially when one considers that there is currently no agreement on the most effective management of these patients and none of the available treatment options have been proven to produce better results over all others or have been clearly shown to have disease-modifying properties. Luckily, one of the nonpharmacological treatments proven to be comparatively more effective for OA patients is exercise. Hydrotherapy was found to produce a small-to-moderate improvement in function and quality of life and a small reduction in pain in osteoarthritic patients. Hydrotherapy is not always available, however, but other exercise modalities have also proven to be useful: strength and aerobic training, range-of-motion exercises, and stretching have beneficial effects in modulating pain, increasing range of motion, reducing or eliminating soft tissue inflammation, inducing relaxation, improving repair, extensibility, or stability of contractile and noncontractile tissues, facilitating movement, and improving function. Tai-chi, a traditional Chinese exercise that enhances balance, strength, and flexibility, has also been shown to be effective in treating knee OA.

A special comment should be made about the cost, availability, and practicality of delivery of the new injective procedures. Among these, platelet-rich plasma therapy, a procedure based

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on the injection of platelet concentrate to encourage tissue regeneration through the release of growth factors contained in the platelet alpha-granules, has been recently gaining popularity as a promising therapeutic option for early OA. However, despite some promising clinical results, the beneficial effect of this procedure is limited over time. Thus, it is important to consider that the high costs, the contraindications for several comorbidities, and the need for specialist centers are major limitations that favor more classic injective procedures. Among these, viscosupplementation seems to offer a clinical benefit, albeit limited over time, without side effects on the joint tissues. However, in patients where the joint has already degenerated, corticosteroid injections can be considered as a cheap option that is easily and widely accessible.

Other more invasive surgical procedures also present specific limitations with regard to cost, availability, or practicality of delivery. Patient comorbidities should also be taken into consideration when contemplating more invasive surgical procedures, as comorbidities can complicate treatment, and logistical problems and the need for assistance during the sometimes long postoperative rehabilitation phase also need to be considered.

How important is therapeutic education in osteoarthritis and why?

Therapeutic education in OA is of major importance. OA is a chronic condition, and long-term management of a disease can be cumbersome. Aside from occasional injections or other medical procedures, patients affected by OA are required to undergo much more difficult changes in their life. In fact, correct management of OA often involves lifestyle adaptation with continuous exercise, frequent physical therapy, and diet modification. None of this is achievable without proper therapeutic education. Patients need to be aware of their condition, of the factors affecting the disease, and of their responsibility in following the correct lifestyle and prescribed therapies. In terms of pharmacological therapy, patients must follow the treatment indications to obtain optimal results, and personal initiatives or treatment adaptations that do not follow the physician’s indications can only lead to lesser benefits. A recent review of the role of exercise in OA management focused on the different methods of treatment delivery, which can entail individual treatment, treatment within a supervised group, or exercise performed at home. No difference was found in terms of the beneficial effects of exercise when patients had received proper therapeutic education and performed the prescribed exercise. However, regular supervision may improve adherence to exercise, which is required to maintain the benefits over time, and a recent study reported that the effects of exercise were better when conducted over more than 12 supervised sessions. Supervised sessions allowed for more therapeutic education and more control over patients, who as a consequence followed their therapies better and thus achieved better results.

Therapeutic education is also of fundamental importance after surgery in order to limit the risk of complications such as infection, or even fatal events, and to optimize treatment. For example, biological implants for tissue regeneration require a maturation phase during which the healing structure has to be protected, and even after metal resurfacing, therapeutic education is mandatory to ensure adaptation of life activities and preservation of the prosthetic joint over time.

How long can nonpharmacological management put off surgical intervention?

Nonpharmacological management can put off the need for surgical intervention, but in this regard every single case must be considered individually. First, it has to be stressed that sometimes it can be counterproductive to put off surgical intervention. This is particularly true when there are clearly recognized predisposing factors that could be addressed surgically. A previous total meniscectomy, joint instability due to ligament rupture, incongruity of the articular surface due to previous intra-articular fractures, misalignment causing overload, and degeneration of an articular compartment are just some examples of clinical conditions for which delaying surgical treatment would only result in a worsening of the joint condition with a worse final outcome.

On the other hand, when there are no clear predisposing factors or when patients present with comorbidities that contraindicate surgical treatments, nonpharmacological management can be used to put off surgical intervention. Of course every case is different, but it is possible to state that in the majority of cases, proper management of OA can delay the need for prosthetic replacement for several years. Lifestyle adaptation with diet modification and exercise, together with other medical treatments such as physical therapy or injections to treat the acute inflammatory OA phases, can improve the clinical condition and delay the need for more invasive surgery.

It is important for the patient to have clear expectations about all the treatment options. Surgery can sometimes be considered by the patient as an easy way to improve their clinical condition, but knowledge of the limitations and risks of surgery can give them the correct perspective in understanding the importance of properly applying nonsurgical management for major beneficial effects and the longest delay before surgical intervention.

Is there any randomized controlled study available on the nonpharmacological approach?

Some randomized controlled studies are available on the nonpharmacological approach, but results are still far from conclusive. Controversial findings, as well as the incredibly high number of variables differing between each study, make comparison of the available studies difficult.
Surprisingly, the definition of OA has not changed since 1986. The diagnosis of knee OA can usually be made from the patient history and physical examination, and includes signs/symptoms of knee pain with stiffness, joint crepitus and functional limitations, and typically an age above 50 years. Diagnosis is confirmed by radiograph demonstrating changes such as osteophytes and joint space narrowing, subchondral bone sclerosis, and cysts, and is graded according to the classification of Kellgren and Lawrence (Kellgren & Lawrence grades II-IV). It appears clear that this definition of OA cannot distinguish between the pathological changes in different tissues. Thus, study populations can be heterogeneous and can respond differently to different treatments, even though they apparently present in the same disease phase.

There is no agreement in the literature on the best treatment option for OA, and this is reflected in clinical practice where treatment is mainly empirical and based on the personal experience of the individual physician. Moreover, leaving aside the contradictory findings of the different studies, it is also difficult to translate the study results into clinical practice because the selected study populations are often a specific category of patients that is rare in the normal population. Patients in clinical practice typically present with more complex clinical situations and with comorbidities and combined treatments.

New imaging techniques are required to better assess the disease phase and to properly classify study populations, and more randomized controlled trials are needed to prove which treatment approach is more suitable for each of the different phases of OA degeneration.

*Can nonpharmacological treatment be combined with pharmacological treatment?*

While it is true that properly applied nonpharmacological treatment can sometimes limit the need for pharmacological treatment, it is also well accepted that combined treatment can often offer a better clinical outcome. In general, the optimal conservative management of knee OA requires a combination of pharmacological and nonpharmacological treatment modalities, and among the nonpharmacological treatments, a combination of different approaches is recommended.

Osteoarthritis Research Society International (OARSI) produced a list of 25 recommendations regarding the treatment of OA. These cover the use of 12 nonpharmacological modalities: education and self-management, regular telephone contact, referral to a physical therapist, aerobic, muscle strengthening and water-based exercises, weight reduction, walking aids, knee braces, footwear and insoles, thermal modalities, transcutaneous electrical nerve stimulation, and acupuncture. A further 8 recommendations cover pharmacological treatment modalities, and finally, 5 recommendations cover surgical modalities: total joint replacements, unicompartmental knee replacement, osteotomy and joint-preserving surgical procedures, joint lavage and arthroscopic debridement in knee OA, and joint fusion as a salvage procedure when joint replacement has failed.

These strategies can be combined according to the specific requirements of the patient with the aim of producing tailored treatment and thus more satisfactory clinical results.

*What can you tell us about life after knee replacement surgery?*

Many options are currently available for knee replacement, from focal metal resurfacing to total prosthetic replacement of the affected joint. Of course, functional improvement and limitations will depend strictly on the implant type as well as the specific characteristics of the patient, and also eventually on the presence of any surgical complications.

In general, this procedure offers a dramatic improvement in the clinical condition. Most patients have minimal pain by 3 months (or sooner) after surgery and return to their normal daily activities. It is not unusual to have occasional muscle aches and persistent (but usually slight) swelling of the knee and extremity for several months, and some patients require a longer time to achieve good and stable results. Depending on numerous factors, a persistent limp is usually expected, but results tend to improve over time.

Unfortunately, 5% of patients will be unsatisfied because of the persistence of pain or the onset of complications. Moreover, it has to be remembered that despite the technological improvements of the last decades, implants still have limited longevity and may require revision surgery. Age is one of the major factors in determining reduced longevity. Younger patients wear out their replacements more quickly than older patients, and this has to be taken into consideration in the management of a patient affected by OA.

In general, prostheses give good results, but they also require adaptation to the activity level of the patient and there are some important risks related to the surgical implant. Thus, when treating a patient affected by OA, it is important to consider all the available options to improve their clinical condition and to keep prosthetic replacement as a last option when functional limitations and symptoms prove to be refractory to less invasive procedures.

The author declares that she has no conflict of interest.
Le but de cette interview est de mieux comprendre le rôle des traitements non pharmacologiques de l’arthrose. L’éventail de traitements est large : adaptation des niveaux d’activité, exercice physique, physiothérapie, injections intra-articulaires, déchargement chirurgical du compartiment articulaire abîmé et prothèse de genou. Tous les traitements visent à améliorer les symptômes, le fonctionnement et donc la qualité de vie ; toutefois, chacun d’entre eux présente ses propres avantages et inconvénients et convient mieux à certaines phases spécifiques de l’arthrose articulaire. Il n’y a actuellement aucun consensus sur la prise en charge la plus efficace de l’arthrose, et aucun des traitements disponibles n’a montré de meilleurs résultats que les autres ou n’a clairement manifesté des propriétés modifiant la maladie. En général, la prise en charge conservatrice optimale de l’arthrose du genou nécessite une association de traitements pharmacologiques et non pharmacologiques. Parmi les traitements non pharmacologiques, l’association des différentes approches est également recommandée. Hormis les considérations sur le choix traitement, il faut aussi tenir compte du fait que l’arthrose est une pathologie chronique et que sa prise en charge à long terme peut être pesante. L’éducation thérapeutique des patients arthrosiques est donc d’une extrême importance. Enfin, les prophèses ont un fort pourcentage de bons résultats mais nécessitent d’être adaptées au niveau d’activité du patient et présentent aussi des risques importants liés à la prothèse implantée. Lorsque l’on traite un patient atteint d’arthrose, il est important de prendre en compte toutes les options disponibles pour améliorer son état clinique et garder la pose d’une prothèse comme dernière solution, lorsque les symptômes et les limitations fonctionnelles ne répondent pas à des procédures moins invasives.
Osteoarthritis was previously considered to be solely a disease of cartilage degeneration. However, it is now recognized that all structures in the joint are affected by the disease, notably subchondral bone, in which characteristic changes occur throughout disease progression. These changes in the bone seem to parallel disease progression and are associated with joint pain. This article focuses on the role played by subchondral bone remodeling in the pathogenesis of osteoarthritis and in the expression of pain in this condition. It examines the evidence for altered osteoblast and osteoclast function and the possible involvement of osteocytes in establishing changes in the subchondral bone environment in osteoarthritis. It also explores the biomechanical and genetic influences that may lead to an altered interaction between bone and cartilage. A large number of genes have been found to be differentially expressed in subchondral bone in osteoarthritis compared with osteoporotic or normal bone, and many of these changes persist in osteoblasts derived from osteoarthritic bone. Relevant questions include how the cellular and molecular changes give rise to structural changes in subchondral bone, including bone marrow lesions; what the evidence is that bone marrow lesions are predictive or even causal of disease progression; and whether treatments targeting the subchondral bone could have efficacy in delaying or reversing degeneration of the overlying articular cartilage.

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tion between articular cartilage and its underlying bone, altered events in the subchondral bone may have significant implications for cartilage health, which validates attempts to treat OA by directing treatment to the subchondral bone.

**Bone shape and osteoarthritis**

It is clear that shape deformities in bone are associated with OA and may either predispose to the disease, or result from it. 
6,7 Malalignment of the knee, with varus or valgus alignment, has been thought to predispose individuals to knee OA. However, as reviewed by Hunter et al, 
8 it is unclear whether malalignment is a risk factor for OA or comes about as a result of the disease, and more longitudinal data are required to determine the link. Congenital dysplasia or dislocation of the hip, whether occurring as a result of perinatal dislocation or congenitally incorrect morphology of the acetabulum or femoral head, can give rise to hip OA because of the lack of congruency of the joint and the concentration of load in a small region of the joint. Genetics may play an important role in OA that has bone deformity as its underlying cause. Waarsing et al 
9 have described a range of shape “modes” for the proximal femur, several of which predispose to OA, but apparently only in carriers of susceptibility alleles of genes that associate with OA. Haverkamp et al 
10 have obtained similar data for the knee, suggesting that a larger tibial plateau area associates with OA. Pincer deformities of the acetabulum and cam deformities of the femoral neck, 
11 which result in various degrees of impingement of the hip joint, are thought to lead to OA. Nichols et al 
12 examined the relationship between cam deformity and the 19-year risk of total hip arthroplasty (THA) for end-stage hip OA. Their intriguing results showed that individuals with THA had a higher prevalence of cam deformity than their respective controls, although the study was limited by small numbers of subjects after exclusions. Further studies in this area are warranted given the prospect that it might be possible to predict the risk of hip OA from hip shape. Two recent studies addressed the important question of whether such deformities are inevitable or whether they may be preventable. It was found that cam deformity seemed to arise from vigorous sporting activity, being more prevalent in elite young basketball players than in age-matched controls. 
11 Similarly, the prevalence of flattening of the femoral head-neck junction was significantly increased in young male soccer players compared with controls, and the presence of a convex prominence (cam deformity) was found only in the soccer players. 
12 These studies highlight the responsiveness of bone to influences such as loading, which has already been well described as a mechanism by which bone strengthens in response to increased demand. 
13,14 They are also a reminder that bone is a dynamic tissue that is constantly undergoing remodeling, 
15 thereby perhaps contributing to OA, but also offering potential points of intervention.

**Microstructural changes in bone in osteoarthritis**

The microstructure of subchondral bone differs in osteoarthritic bone compared with nonosteoarthritic bone, particularly with respect to the subchondral plate and adjacent trabecular bone, but also in regions more distal from the affected joint. 
16,17 For example, Kumarasinghe et al 
18 reported increased bone volume fraction in cancellous bone from the intertrochanteric region in individuals with OA compared with those with normal or osteoporotic bone, with increased trabecular number and decreased trabecular spacing. Reduced hardness of trabecular bone from the femoral head was also noted in hip OA compared with normal subjects, 
19 probably due to decreased mineralization of the bone in OA. 
20 These changes combine to produce bone that is stiffer and stronger than normal or osteoporotic bone. 
21 It is not known at which stage of human disease these changes appear, and whether they are, in some way, causative of the disease process or simply describe it. For the most part, animal models show that changes in the subchondral bone occur in parallel with cartilage degradation. 
21 Longitudinal mouse studies that used high-resolution imaging to investigate joints in a mouse strain that spontaneously develops knee OA compared with one that does not showed that susceptible mice developed more trabecular bone in a region-specific manner, and particularly in the tibial compartment, in parallel with arthritic changes in the articular cartilage. 
22 In addition to the generalized changes in subchondral bone in OA, areas of subchondral bone that appear bright with MRI, which are termed BMLs, are commonly observed in both established OA and early OA, but rarely in symptom-free individuals. 
23,24 BMLs have not been extensively characterized, but they arise in regions of predicted high loading and contain abnormal bone with areas of osteocyte death and areas of bone sclerosis with reduced mineral density. 
25 Subchondral bone attrition 
26 and repair of fractured trabeculae have also been observed. 
27 BMLs are interesting clinically due to the fact that longitudinal studies have shown that their presence is a potent risk factor for structural deterioration in knee OA 
28,29 and for future joint replacement. 
30 BMLs have been shown to be dynamic, increasing and decreasing in size, and they have

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**Selected abbreviations and acronyms**

- ACLT: anterior cruciate ligament transection
- BML: bone marrow lesion
- ES/BS: eroded surface/bone surface ratio
- MRI: magnetic resonance imaging
- OA: osteoarthritis
- OARSI: Osteoarthritis Research Society International
- OPG: osteoprotegerin
- OS/BS: osteoid surface/bone surface ratio
- TGFβ: transforming growth factor β
- THA: total hip arthroplasty
- WOMAC: Western Ontario and McMaster Universities Osteoarthritis index
also been found to disappear over a 2-year period. In a community-based population of older males and females, similar proportions of BMLs were found to worsen and improve (assessed by measuring maximal area). Importantly, a change in BML size was associated with changes in pain, perhaps linking fluctuating knee pain to BML changes, at least in individuals with early-stage disease. Enlargement of BMLs has been strongly associated with increased cartilage loss. Subchondral cysts, which are characteristic of established and severe OA, arise at the same sites as BMLs. A number of studies have indicated possible causal factors for BMLs, including mechanical loading, dietary fatty acid intake, and total serum cholesterol and triglycerides.

Bone remodeling in osteoarthritis

As stated, bone is constantly being remodeled, and this may have special significance in OA in ways that require more attention. Understanding bone remodeling in the particular context of OA is complex. The topic was recently the subject of an excellent review by Burr and Gallant, who cited evidence for increased remodeling, accompanied by increased vascularity, in the subchondral bone in early OA. By contrast, late-stage disease is characterized by reduced bone resorption, with a bias toward bone formation. In addition to these temporal variations, it is likely that bone remodeling varies spatially within the joint; for example, medially versus laterally in the knee. There is histological and biochemical evidence of increased bone remodeling in subchondral bone containing BMLs. Increased subchondral bone remodeling as detected by bone scans has been described in established OA, where it has been reported to joint space narrowing.

In contrast, a report by Berry et al concluded that higher levels of bone remodeling (assessed by serum bone turnover markers) is associated with reduced cartilage loss (assessed by MRI). It is difficult to determine whether changes in bone turnover are a cause or effect in human OA; however, work in Hartley guinea pigs showed that subchondral cancellous bone was fragile before the onset of cartilage degeneration. In the rat anterior cruciate ligament transection model of OA, increased subchondral bone resorption was associated with early development of cartilage lesions, which preceded significant cartilage thinning and subchondral bone sclerosis.

At the level of the bone cell, remodeling is a function of the actions of osteoclasts, which resorb bone, and osteoblasts, which are the bone-forming cells. The activities of both of these cell types are regulated by osteocytes embedded within the bone matrix. There is good evidence that osteocytes detect damage within the mineralized bone matrix and direct its repair by initiating targeted osteoclastic resorption of the affected bone, and in OA, there is evidence of increased microdamage and microfractures in subchondral bone in overloaded areas of the joint. Recent evidence suggests that osteocytes are the major source of the osteoclast differentiating cytokine, receptor activator of nuclear factor κ-β ligand (RANKL), in mature bone. Osteocytes also produce sclerostin, a Wnt inhibitor that negatively regulates bone formation. Individuals and animals deficient in sclerostin show bone overgrowth. Sclerostin appears to mediate the actions of a number of factors that influence bone formation, so that loading of bone, a known anabolic influence, decreases sclerostin expression in bone, and unloading of bone, which is catabolic for bone, increases its expression. Both of these conditions might apply at different times during the progression of OA. Interestingly, increased sclerostin expression has been observed in cartilage overlying sclerotic bone, while the latter by contrast shows decreased sclerostin expression. Since osteocytes have such a strong influence on bone metabolism and turnover, it may be an important finding that in osteoarthritic subchondral bone, osteocyte morphology was altered, showing rough and rounded cell bodies with fewer and disorganized dendrites compared with the osteocytes in control samples. In addition, and this has been particularly noted in BMLs, there is evidence of osteocyte apoptosis, which, as stated, can be a stimulus for osteoclastic resorption and bone turnover.

Differential gene expression in osteoarthritic bone

The structural changes in osteoarthritic bone follow changes in bone cell activity, which are in turn driven by, and evidenced as, altered gene expression in osteoarthritic bone compared with bone from age- and sex-matched controls or osteoporotic individuals. The opportunity to investigate bone in OA is essentially limited to sampling during joint replacement surgery in end-stage disease, and the gene expression observed at this time likely represents the decrease in remodeling described in late-stage OA. In fact, both the gene and protein expression that have been described in human late-stage OA are largely consistent with the reduced bone turnover, sclerosis, and lower bone mineralization that have been described in OA bone tissue at this time. Kuliwaba et al measured RNA extracted from the cancellous bone in the intertrochanteric region of the proximal femur, a site distal to the articular surface of the femur, and compared patients with end-stage OA with age-matched autopsy controls. Differential gene expression was found in OA bone, which had the hallmarks of reduced inflammatory cytokines and bone resorption markers and increased bone formation. Messenger RNA species encoding interleukin (IL)-6 and IL-11 and RANKL were significantly less abundant in the OA group, while osteoprotegerin (OPG) mRNA expression was no different from controls. In a separate study, an additional increase in the anti-osteclastogenic cytokine interferon gamma was also observed in OA. Both RANKL mRNA levels and the ratio of RANKL:OPG mRNA were strongly associated with eroded surface/bone surface ratio (ES/BS) and osteoid surface/bone surface ratio (OS/BS) in trabecular bone from control individuals; the former would be expected for this cytokine, which is a potent driver of bone resorption, and the latter is likely due to the fact that bone resorption and formation are coupled in healthy adult bone.
Intriguingly, these relationships were not apparent in osteoarthritic bone, suggesting that bone turnover is regulated differently in OA. In terms of bone formation, osteocalcin mRNA expression was significantly greater in OA and, curiously, increased significantly with age in the OA group but not in controls. In addition, there was a significant positive correlation between the osteocalcin mRNA levels and OS/BS in OA bone, which was not seen in the control cohort. Work by the same group showed elevated alkaline phosphatase, osteocalcin, osteopontin, and COL1A1 (collagen, type I, alpha 1) and COL1A2 (collagen, type I, alpha 2) mRNA in osteoarthritic bone compared with control, which the authors suggested reflects an increase in osteoblastic biosynthetic activity in OA.

Hopwood et al performed gene microarray analysis on bone from the same region of the femur, and identified a large number of differentially expressed genes in OA compared with control or osteoporotic bone. A substantial number of the top-ranking differentially expressed genes are known to play roles in bone formation, and many of these genes are targets of either the Wnt or transforming growth factor β (TGFβ) bone morphogenetic protein signaling pathways. These findings are consistent with the increased amounts of insulin-like growth factor types I and II and TGFβ protein measured in osteoarthritic bone from the iliac crest. This latter result, and the findings from bone derived from the intertrochanteric region, are consistent with both increased anabolic stimulus in osteoarthritic bone and the notion that bone metabolism may be systemically disturbed in OA.

**Osteoblasts from osteoarthritic bone**

Gene expression has also been explored in osteoblasts taken from osteoarthritic subchondral bone. Interestingly, these cells appear to retain their phenotypic differences from control cells in culture. Thus, one group showed that cultured OA osteoblasts produced a similar degree of mineralization to control cells, but with dramatically variable calcium:phosphate ratios compared with control osteoblasts and normal bone (approximately 1.6). A second group showed that mineralization by OA osteoblasts was decreased compared with control osteoblasts, which they found to be due to a threefold higher COL1A1:COL1A2 mRNA ratio in the OA cells. This finding in cells was similar to the differential expression of these genes in osteoarthritic bone. Alkaline phosphatase and osteocalcin levels were also found to be elevated in OA osteoblasts compared with normal osteoblasts, whereas osteopontin levels were similar. In this study, the authors obtained evidence that TGFβ1 levels are approximately fourfold higher in OA osteoblasts than in normal osteoblasts, and that inhibiting TGFβ1 in OA osteoblasts corrected the abnormal COL1A1:COL1A2 ratio and increased cell mineralization. It was subsequently shown that the increased TGFβ1 in OA cells induces increased Dickkopf-related protein 2 (DKK-2), and that silencing of either TGFβ or DKK2 in these cells normalized the OA phenotype, including the decreased mineralization of OA osteoblasts.

Massicotte et al performed measurements of conditioned media from osteoblasts derived from osteoarthritic subchondral bone, and reported two subgroups of cells based on production of IL-6 and prostaglandin E2, while TGFβ levels were increased in all osteoarthritic osteoblasts compared with normal osteoblasts. Kumarasinghe et al performed an extensive analysis of gene expression in primary osteoblasts derived from OA and control femoral bone. They found that the dysregulated expression of TWIST1 (twist-related protein 1), TGFβ1, and SMAD3 (mothers against decapentaplegic homolog 3) mRNA observed by Hopwood et al in OA bone is also present in OA osteoblasts when these cells are cultured ex vivo, and they proposed that at least part of the etiology of OA is due to altered intrinsic properties of the osteoblasts.

**Directing treatments for osteoarthritis to the subchondral bone**

It is clear that changes in subchondral bone parallel the progression of OA and may even be causally involved. The subchondral compartment may therefore be a treatment target to delay or prevent progression of the disease. Since this compartment is richly innervated, and cartilage is devoid of nerves, bone is also a legitimate treatment target for joint pain. However, treatments designed to normalize the bone changes in OA are controversial, largely because the promise of efficacy seen in animal models has not been matched by human studies. It would seem reasonable that treatment with antiresorptive agents in early disease might be effective, since this phase of the disease is characterized by increased bone remodeling. Accordingly, in two rat models of knee OA, the bisphosphonate alendronate suppressed both subchondral bone resorption and the later development of OA symptoms in the knee joint. Similarly, calcitonin reduced the levels of circulating bone turnover markers and the severity of OA lesions in the dog model of anterior cruciate ligament transection (ACLT). Kadri et al used OPG to block RANKL-mediated bone resorption and remodeling in a mouse meniscectomy model of OA, and observed protection from meniscectomy-related bone loss, lower OA scores, and reduced ADAMTS-4 and ADAMTS-5 expression following meniscectomy. In a high bone turnover version of the same mouse model, pamidronate dramatically preserved the bone mass and reduced the Osteoarthritis Research Society International (OARSI) score while at the same time almost normalizing the expression of ADAMTS-4 and ADAMTS-5 in the overlying joint cartilage.

Such marked effects of antiresorptive agents have not been consistently observed in human trials of antiresorptive agents in OA subjects, where symptom relief, radiographic joint space narrowing, or Western Ontario and McMaster Universities Arthritis index (WOMAC) were used as end points, and it has been argued that such agents are unlikely to show efficacy in late-stage OA because bone resorption is already suppressed at this stage. Interestingly, results of a trial in which
postmenopausal women were treated with strontium ranelate indicated that subjects with early OA (C-terminal crosslinked telopeptide type II collagen [CTX-II] was used as a surrogate marker of disease) obtained the greatest benefit, again in terms of CTX-II reduction. It is thus clear that earlier defining bone pain caused by elevated levels of bone remodeling, since this is the case in the high bone turnover states of Paget’s disease, osteogenesis imperfecta, and cancer-induced bone pain. The results of the trial by Laslett et al suggest that this is a possibility in OA.

Conclusion
Changes in the bone of articulating joints are apparent from the time of the earliest symptoms of OA, and are due to altered bone structure, altered biochemistry, and altered biomechanics, which in turn cause altered gene expression in bone. This altered bone remodeling needs to be better understood temporally, spatially, mechanistically, and molecularly, so that informed treatments can be developed for application at a time point when efficacy can be achieved, starting as early in the disease course as possible. In the evaluation of approaches that target the bone in OA, end points will be required that are based on better imaging and that are much more informative of all the compartments of the joint, cartilage, synovium, tendon and muscle, and bone.

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Keywords: antiresorptive; gene expression; osteoarthritis; remodeling; subchondral bone

FOCUS


New therapeutic perspectives in osteoarthritis are focused on blocking the degradative process by inhibiting tissue remodeling in the bone and cartilage and inflammation of the synovial membrane. None of the so-called slow-acting drugs that are currently available for the management of osteoarthritis can be considered to be targeted treatments. A great hope surfaced after initial trials with anti–nerve growth factor therapy showed a dramatic effect on pain in patients with knee osteoarthritis. Unfortunately, trials were later stopped because of unexplained rapidly destructive arthropathies. Biotherapies involving interleukin-1 blockers have been used in knee osteoarthritis, but so far have shown no efficacy on pain. Biotherapy for hand osteoarthritis involving the use of tumor necrosis factor blockers to slow down disease progression has failed. Nitric oxide inhibitors also failed to demonstrate a chondroprotective effect in a large trial involving patients with knee osteoarthritis. Inhibitors of enzymes involved in cartilage matrix degradation are in a preclinical phase of development, but constitute an appealing approach. Targeting of subchondral bone is also a promising approach. Although previous chondroprotective trials using bisphosphonates have produced negative results, a recent large trial with strontium ranelate showed diminished joint space narrowing over 3 years of follow-up. Another therapeutic approach currently under consideration is stimulation of chondrocyte anabolism. Intra-articular injection of growth factors is in the initial development phase. Finally, a new lubricant called lubricin has shown very attractive results in animal models.
whole organ, the joint.2,3 The tissue changes observed in osteoarthritis include not only cartilage degradation, but also sclerosis of subchondral bone, osteophyte formation, and to varying degrees over time and space, inflammation of the synovial membrane.3 The concept of osteoarthritis as organ failure with multisynovial disease opens up novel therapeutic perspectives whereby not only the cartilage damage can be targeted, but also synovitis and remodeling of subchondral bone, the latter two participating in a major way in the destruction of cartilage.4,5

Current treatments for osteoarthritis, as defined by the latest international consensus conferences, are essentially aimed at controlling the painful symptoms, thereby reducing the disability that is essentially related to the pain in osteoarthritis.6,7 The real therapeutic goal for osteoarthritis in the coming years will be to find a treatment that can permanently reduce cartilage destruction.

Data on the currently available treatments
For the purposes of slowing down the progression of osteoarthritis, a therapeutic class of drugs known as slow-acting anti-arthritic agents is used. These drugs include derivatives of avocado and soya, diacerein, chondroitin sulfate and glucosamine sulfate, and hydroxychloride salts. The status of some of these molecules is that of a nutrient rather than a true medicine. These molecules have shown a favorable risk-benefit ratio in lower limb osteoarthritis, but their analgesic effectiveness remains modest and controversial.7,8 A recent trial using 800 mg of chondroitin sulfate for osteoarthritis of the fingers showed that it could significantly reduce the painful symptoms over a period of 6 months.9 In terms of chondroprotection, these molecules have been shown in various trials to slow the narrowing of the joint space by about 0.1 mm per year, especially in osteoarthritis of the knee, and to reduce the number of patients defined as rapid progressors.8 Such a minimal annual slowdown still needs to be translated in terms of clinical relevance. The “end point” could be, for example, whether this annual slowdown can delay the need for the implementation of a total prosthesis of the treated joint.10

Targeting proinflammatory mediators and other players in osteoarthritis

◆ Biotherapy
Biotherapy involves specifically blocking a molecule (cytokine or growth factor) involved in the inflammatory and/or painful process in osteoarthritis.11

◆ Targeting pain by inhibiting nerve growth factor
Nerve growth factor (NGF) is a molecule directly involved in the pathways responsible for pain transmission.12 This molecule was first described in the nervous system. It acts by means of two tyrosine kinase-type receptors.12 By binding to its receptor, it may modify the phosphorylation of vanilloid-like pain receptors (nociceptors).12

NGF has been identified in the joint, particularly the osteoarthritic joint, and it is present at detectable levels in synovial fluid.13 It was therefore logical to investigate the use of an inhibitor of NGF as a potential treatment. Tanezumab (TNZ) is a fully human monoclonal antibody directed against NGF; it was used in a randomized trial versus placebo that involved perfusions every 8 weeks at different doses in patients suffering from painful knee osteoarthritis (n=450). The results at 16 weeks were impressive, with a very substantial reduction in pain of between 45% to 62% in the TNZ groups compared with 21% in the placebo group.14 Unfortunately, in addition to some adverse neurological side effects, phase 3 clinical trials revealed an increased number of rapidly destructive arthropathies (similar to neurological arthropathies) that led to the implementation of prostheses, resulting in the suspension of trials with this type of antibody.15 Use of nonsteroidal anti-inflammatory drugs in conjunction with anti-NGF seems to increase this risk. Since the publication of a recent report by the US Food and Drug Administration, however, the use of NGF inhibitors under specific conditions and without the concomitant use of nonsteroidal anti-inflammatory drugs has again been authorized.

◆ Biotherapies targeting proinflammatory cytokines
Osteoarthritis is in part an inflammatory disease, as indicated by its name. The inflammation is localized mainly in the synovial membrane, but also in the subchondral bone and cartilage, and involves a cascade of proinflammatory mediators (fragments of the matrix, cytokines, complement components).16 These mediators not only contribute to the degradation of the cartilage matrix during attacks of synovitis, but are also involved in pain transmission pathways.17,18

Two proinflammatory cytokines play a major role in osteoarthritis: interleukin 1β (soluble form of interleukin 1 [IL-1]) and tumor necrosis factor-α (TNF-α).2,16 Through in vitro studies, and later with the use of animal models in vivo, it was demonstrated that IL-1 is a key molecule favoring cartilage degradation, inhibition of chondrocyte synthesis, and apoptosis.16 Use of an IL-1 inhibitor through local intra-articular adminis-

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**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>DORA</td>
<td>Digital Osteoarthritis in Refractory hand OA (study)</td>
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<tr>
<td>FGF18</td>
<td>fibroblast growth factor 18</td>
</tr>
<tr>
<td>IL-1</td>
<td>interleukin 1</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>NGF</td>
<td>nerve growth factor</td>
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<tr>
<td>NO</td>
<td>nitric oxide</td>
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<tr>
<td>TIMP</td>
<td>tissue inhibitor of metalloproteinase</td>
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<tr>
<td>TNF-α</td>
<td>tumor necrosis factor-α</td>
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<tr>
<td>TNZ</td>
<td>tanezumab</td>
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<tr>
<td>WOMAC</td>
<td>Western Ontario and McMaster Universities Arthritis index</td>
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The second randomized trial compared repeated systemic injections (by subcutaneous injection) of a monoclonal anti-body blocking the type 1 receptor of IL-1 with placebo. The injections were administered monthly. Again, up to 3 months, IL-1 inhibition demonstrated no significant analgesic effect. In addition, constant neutropenia was reported and a case of death from severe pneumonia was also observed. On the other hand, functional magnetic resonance imaging (MRI) demonstrated changes in the subgroup of patients showing a beneficial effect from IL-1 inhibition.

From these two trials, we can conclude that at present, inhibition of IL-1 has not enabled observation of an analgesic effect in knee osteoarthritis. However, IL-1 seems to be a good therapeutic target. Thus, in the future, it will be necessary to think about modes of administration, including the intra-articular mode, which can prolong the action of this inhibitor, and to see whether prolonged inhibition of this cytokine can delay the progression of osteoarthritis.

The second potentially interesting molecule to target is TNF-α, which has an important proinflammatory effect and whose effect on cartilage degradation potentiates that of IL-1. Two randomized trials have been conducted on two different inhibitors of IL-1 versus placebo in patients with knee osteoarthritis. We conducted the first biotherapy trial in osteoarthritis using an IL-1 antagonist (anakinra) administered by a single intra-articular injection (dose of 50 mg or 150 mg) versus a placebo injection of physiological saline. In this trial, there was no significant difference in the Western Ontario and McMaster Universities Arthritis Index (WOMAC) global score or level of pain at 1 month, 3 months, and 6 months. However, at 4 days, there was a small but significant difference in the level of pain reported in the patient group that received 150 mg of the IL-1 receptor antagonist. In fact, pharmacokinetic studies have shown a very short half-life of about 6 hours for IL-1 receptor antagonists in serum, which is incompatible with having a residual effect on pain.

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TNF-α is mainly used as a target in digital osteoarthritis, which can involve a more painful and inflammatory condition called erosive osteoarthritis. Systemic administration of a TNF-α inhibitor is logical in this polyarticular form of osteoarthritis. Repeated subcutaneous injections of adalimumab produced no evidence of a decrease in the structural evolution of digital osteoarthritis compared with placebo over a period of 1 year. Only the subgroup of patients with clinically detectable effusion at baseline at the interphalangeal joints showed a lower incidence of new erosions. In other words, it seems that anti-TNF may be active on the structural progression of the disease in a subgroup of patients suffering clinically from a more inflammatory disease. The French study, Digital Osteoarthritis in Refractory hand OA (DORA), aimed to assess the symptomatic effect of two injections of a monoclonal antibody directed against TNF-α.

**Nitric oxide inhibition**

Nitric oxide (NO) is a gas that plays many physiological roles, particularly in terms of regulation of arterial vasodilation, but it may also play a deleterious role when produced in excess. It has been demonstrated that NO produced in excess during osteoarthritis could contribute to cartilage destruction through protein nitrosylation, but could also favor apoptosis of chondrocytes through combined action with free radicals. It was therefore logical to consider that inhibition of NO could reduce the progression of osteoarthritis. A recent randomized placebo-controlled trial used two doses of an inhibitor of NO administered orally (50 mg and 200 mg). The trial investigated chondroprotection in knee osteoarthritis, with the main outcome criterion being evolution of radiographic joint space narrowing observed at 2 years. This study showed no difference in the overall study population at 2 years in terms of reducing progression of radiographic joint space narrowing. There was only a trend favoring the molecule in the subgroup of patients with a Kellgren-Lawrence grade superior to 2 at 48 weeks.

To sum up, this trial does not allow us to conclude on the efficacy of NO inhibition in reducing the progression of knee osteoarthritis.

**Inhibition of metalloproteases and enzymes involved in cartilage degradation**

Degradation of the extracellular matrix of cartilage is due to the increased activity of enzymes such as metalloproteases, as well as aggrecanase enzymes and a number of serine proteases. These enzymes are activated in situ by the action of proinflammatory mediators such as cytokines. It seems logical, therefore, to block these enzymes in order to slow the progression of osteoarthritis. The first trials to be conducted in this area used nonselective inhibitors with many side effects, including skeletal muscle disorders and tendinitis, which led to discontinuation of their production. Highly selective inhibitors are currently available, however, including matrix metalloproteinase (MMP)-13 inhibitor. The major role of MMP-13 has been well demonstrated in knockout mouse models of osteoarthritis. In an experimental model of osteoarthritis in dogs, a selective inhibitor of this enzyme showed a convincing chondroprotective effect. The use of these kinds of inhibitors could thus be tested clinically in future. Similarly, one can consider the use of natural inhibitors of these metalloproteases, which
are designed as tissue inhibitors of metalloproteinase (TIMPs). Indeed, it has already been demonstrated that intra-articular injections of TIMP3 could slow the evolution of degenerative lesions in experimental animal models of osteoarthritis.35

**Targeting subchondral bone**

There are many arguments in favor of a major role for subchondral bone in the genesis and progression of degenerative joint disease (see article by Professor David Findlay in this issue). In animal models, there are early lesions of the subchondral plate (microcracks) in vivo, with accelerated bone remodeling. In situ, there is a break in the bone-cartilage calcified dividing line, leading to neovascularization of the deep layers of cartilage and a change in chondrocyte phenotype under the influence of factors such as vascular endothelial growth factor. In vivo, MRI has revealed subchondral bone lesions (bone marrow lesions) in the form of a hypersignal next to the affected cartilage, which can predict the progression of knee osteoarthritis. Finally, radiographs reveal late subchondral sclerosis.36,37

The use of treatments designed to slow remodeling of the subchondral bone appears appropriate in order to preserve the adjacent cartilage. The use of parathyroid hormone (either in a curative or preventive capacity) in an experimental model of osteoarthritis in mice has shown very promising results in terms of chondroprotection.39 A few clinical trials have been conducted using various anti-osteoporotic drugs to examine their possible chondroprotective effect.

**Use of bisphosphonates**

The use of risedronate at different doses in a randomized trial versus placebo conducted over 2 years was not able to demonstrate any chondroprotective effect.39 The poor progression in patients included in this study may account for the failure of bisphosphonates. However, decreased urinary levels of collagen CTX2 (Human C-telopeptide of Type II Collagen) were observed in this trial, perhaps indicating a reduction in joint remodeling.39

A recent randomized placebo-controlled trial used a single perfusion of zoledronic acid in 30 patients with symptomatic osteoarthritis of the knee and subchondral edema revealed by MRI.40 At 6 months, there was a significant decrease in pain and bone edema observed on MRI in the patients receiving zoledronic acid. However, at 12 months, there was no longer any significant difference.40

**Use of oral calcitonin**

A large-scale trial involving nearly 1200 patients with knee osteoarthritis compared the use of two doses of oral calcitonin with placebo. Patients were followed up over a 2-year period. The main purpose of the study was to assess the ability of oral calcitonin to slow joint space narrowing as assessed by a standard knee x-ray.41 On the basis of this criterion, the test was negative; however, patients also underwent MRI. A significant difference in cartilage volume favoring calcitonin was observed at 12 months compared with placebo. It is difficult to interpret the observed effect solely on the basis of MRI data. Moreover, the rate of side effects observed with calcitonin was very high and led to patient discontinuation on the grounds of intolerance in nearly 20% of cases.41

**Use of strontium ranelate**

The use of strontium ranelate for OA treatment has two advantages; on the one hand, there is an indirect effect on bone, but there is also a potential direct effect on cartilage. Indeed, the use of strontium ranelate specifically (the same effect was not observed with calcium ranelate) produced increased synthesis of proteoglycans in vitro, and a synergistic effect with insulin-like growth factor-1 on the anabolism of chondrocytes in vitro.42 On the basis of this observation, the largest-ever chondroprotection study was conducted using two doses of strontium ranelate (1 g and 2 g) compared with placebo over a period of 3 years in patients with symptomatic knee osteoarthritis.43 Over 1600 patients were recruited. The proportion of patients who completed the study was approximately 55% and 60%, respectively, which is consistent with what has been observed in previous trials.44 The results of this trial were positive, and showed an annual slowdown of 0.14 mm in the group receiving 1 g of strontium ranelate and 0.10 mm in the group receiving 2 g of strontium ranelate. In addition, the group of patients defined as radiological progressors (ie, those with a loss of more than 0.5 mm over the 3-year period) was significantly reduced in the strontium ranelate groups compared with placebo: 33% in the placebo group compared with 22% and 26% in the strontium ranelate groups, respectively.44

Finally, for the highest dose of 2 g, a combined effect on pain was also observed, especially in patients experiencing a painful condition as well as rapid progression of their disease.44 This large-scale study opens up interesting perspectives, and could eventually lead to the use of anti-osteoporotic agents such as strontium ranelate for the prevention of cartilage loss.

**Stimulating anabolism by the use of growth factors**

There is another interesting therapeutic option whose aim is not to limit the destruction of cartilage, but rather to favor cartilage repair, even when it is naturally weak. The possibility of direct intra-articular injection of growth factors (bone morphogenetic protein-7 or fibroblast growth factor 18; FGF18) is still in its early stages, and phase 1/2 trials are currently ongoing.45,46 One study, published only as an abstract, used intra-articular injections of FGF18 (either a single injection or two cycles of three intra-articular injections) in knee osteoarthritis.46 There was no evidence of a slowdown in the narrowing of the joint space compared with placebo, but there was a benefit in terms of cartilage volume gain as assessed by MRI at 1 year.46 With regard to local injections of either platelet-rich autologous plasma or autologous conditioned serum, the
References

Conclusion
A better understanding of the physiopathogenesis of degenerative disease in osteoarthritis, particularly the involvement of different tissues of the joint such as the synovial membrane and the subchondral bone, has allowed us to consider some very interesting prospective therapeutic options. Combination of different treatments may also eventually be considered, which at different time points could target the synovial membrane, stem cell cartilage repair, and limitation of long-term remodeling of the subchondral bone. Nevertheless, it will also be necessary to demonstrate that modulatory effects on these structural components can also have an impact on and a clinical relevance for a “hard” criterion, such as delaying the need for total joint replacement surgery.

Keywords: anti-osteooporotic drug; biotherapy; cartilage; metalloprotease; nitric oxide; osteoarthritis; strontium ranelate
By inventing the film camera, and perforations to advance the film through a camera and a projector, France, through the Lumière brothers, gave birth to the cinema. On 19 March 1895, they produced the first footage ever made, albeit on an admittedly dull topic, that of workers leaving a factory after their day’s work. “Touch of France” looks at the early history of the motion picture and its developments in the fields of science and medicine (Christian Régnier), and at the gigantic effort to preserve the legacy of the cinema, with the French Cinémathèque founded by Henri Langlois (Isabelle Spaak). And remember, the love affair between France and the cinema is still alive and kicking: do “The Artist” and Audrey Tautou mean anything to you?
In the 1870s, a forerunner of the motion picture settled a bothersome question. Does a galloping horse ever become airborne? More prosaically, are all four of its hooves ever off the ground at the same time? It fell to the English photographer Eadweard Muybridge to find the answer. Hired by a former governor of California and racehorse owner, Muybridge placed glass-plate cameras along the edge of a race track. As the horse passed each camera it broke a thread and triggered the shutter, thus generating a series of photographs. Muybridge copied these as silhouettes onto a disc and, using his invention the zoopraxiscope, showed that there was indeed “unsupported transit,” a fleeting moment when the horse was airborne. The zoopraxiscope later came to be regarded as an early movie projector, and with it Muybridge wrote a page in the history of early cinematography. So too did the French astronomer Jules Janssen, with his “photographic revolver,” which he used in Japan in 1874 to record the transit of Venus across the face of the sun. And above all there was Étienne-Jules Marey, a French doctor and physiologist who developed the chronophotograph and other instruments for pioneering analysis in humans and animals of locomotion and physiological processes like blood flow, breathing, and the beating heart. These and other pioneers were driven by their thirst for scientific understanding. Others, meanwhile, had their eyes on the immense commercial and artistic potential of the new technique of motion pictures. At the close of the 19th century, the American engineer Thomas Edison, the French industrialists Louis and Auguste Lumière, and the French illusionist Georges Méliès joined the adventure of the new cinematography. Industrial logic, the drive for profitability, and the lure of wealth drove them, and led to clashes with scientists who saw cinematography purely as a research and educational tool. From its beginnings in the laboratories of science, cinema had become a show, a leisure activity accessible to everyone. Dubbed the seventh art (after architecture, sculpture, painting, music, poetry, and dance) by the Italian film theoretician Ricciotto Canudo, the motion picture was able to portray all aspects of life whether scientific or fictional.

Medicographia. 2013;35:237-245 (see French abstract on page 245)
Today’s cinemagoers, accustomed as they are to computer-generated three-dimensional images full of sound and fury, would have scant regard for a 45-second silent film with the humdrum title *Workers Leaving the Lumière Factory*. Yet motion pictures were born that March day in 1895, when the Lumière brothers Louis and Auguste showed their film to a gathering of scientists at the Grand Café on the Boulevard des Capucines in Paris. Sons of a manufacturer of photographic equipment, the Lumières screened the film using their “cinematograph,” which combined a camera and projector to recreate movement. Not everyone present was thrilled. Étienne-Jules Marey, the President of the Academy of Sciences, was sickened by what he saw: intellectual theft. The Lumière brothers’ projector, he said, was his invention, the chronophotograph, hijacked and poorly disguised by the addition of a cam for perforated films. Marey was interested solely in science and biology, and was hostile to the commercial exploitation of moving pictures.1,2 As a pioneer of the analysis of movement, he developed a chronophotographic projector using unperforated film to record and study normal and abnormal human gait, the beating of a perfused frog heart, airborne birds and insects, swimming rays, even the movement of smoke trails.

Cinema, a godsend for showmen and industrialists

The principle of moving images was not new and various animation devices were invented in the middle years of the 19th century. The thaumatrope, beloved of every child, relies on the persistence of vision to combine two separate images into one: a bird on one side of a spinning card, its cage on the...
other. The phenakistiscope, zootrope, kinetiscope, and praxinoscope (the latter invented in France in 1877 by Charles-Émile Reynaud) all created the illusion of movement, and in 1891 Thomas Edison patented his kinetoscope and a camera, the kinetograph, which used perforated 35-mm film. The kinetoscope’s continuous lighting offered closed loop images for one viewer at a time. This wealth of ideas and inventions knew no limit; nor, it should be added, did intellectual property disputes or wrangling over patent applications (nearly 150 in France in 1896).1

In December 1895, the Lumière brothers screened what was probably the first ever comedy film. L’Arroseur Arrosé (The Sprinkler Sprinkled) was shown to an audience of 33 in the Indian Salon of the Grand Café, on the boulevard des Capucines in Paris. The entry charge was 1 franc—to put this into context, the salon could be rented for a whole year for 30 francs. The success was immediate, and lasting as word of mouth ensured that for weeks on end people came to the film show at the Grand Café—between 2000 and 2500 every day. Emboldened by their triumph, the Lumière brothers trained operators and sent them on filming trips around the world, while use of their cameras spread among fairground cinemas. Among those at the first screening of The Sprinkler Sprinkled that December day was the illusionist Georges Méliès. He quickly acquired a camera and in 1897 opened a film studio at Montreuil-sous-Bois, near Paris, where he founded his company Star-Film. A pioneer in special effects, Méliès made one thousand 125-meter (4-minute) films, and won worldwide acclaim with his masterpiece Le Voyage Dans la Lune (A Trip to the Moon). Méliès trod not the cinematic road of the quest for knowledge, but that of a storyteller making films for the general public.1
Industrialists, too, sought to exploit the potential of moving images. Georges Demeny, Marey’s assistant at the physiology annex of the Collège de France, started out studying the movements of the mouth during speech. In May 1892, at the first International Exhibition of Photography in Paris, he presented thirty or so moving images mouthing the phrase “je vous aime” (I love you). Demeny also invented the phonoscope, which recorded both images and sound, to teach deaf-mutes how to speak. He soon recognized, though, the commercial potential of his invention, changed tack, and set up a company (Société Générale du Phonoscope) to focus on the industrial exploitation of his process.1

Using an improved version of his phonoscope, Demeny then filmed short photograms, “living portraits” of people uttering a few words, and everyday scenes unrelated to his original scientific endeavors. The breach with Marey, who was opposed to the commercial exploitation of moving pictures, was not long in coming, and in 1894 Demeny was forced to resign from the Collège de France. Unfazed, Demeny is believed to have filmed the national funeral of Louis Pasteur on 5 October 1895 using 6-mm film, and two years later invented the 35-mm version of his camera. Unversed in the ways of business, Demeny sought help from Léon Gaumont, the founder of the French production company L. Gaumont et Cie, which manufactured projection equipment and cameras. Demeny fared badly in the venture and his process was bought by Gaumont, thus bringing to an untimely end this first marriage between science and industry.1

**Birth of the French scientific film**

In 1898, Dr Eugène Doyen, a well-known surgeon, paid someone to film him performing a hysterectomy and a craniotomy (his specialties) in his private clinic on the rue Piccini in Paris. When his surgeon colleagues of the Academy of Medicine balked at showing his films in public, Doyen himself paid for their projection. They showed medium-close shots, with no décor, and were intended for teaching purposes, though Doyen did not hesitate to show them to an “impressionable” public. The surgeon Jean-Louis Faure, another pioneer of surgical films, said of Doyen’s films that they were of great educational value, but tended to showiness, which, he felt, marred the demonstration of the surgical technique.

A few years later Doyen hired a camera operator to film his surgical separation of Doodica and Radica, conjoined twins who starred in Barnum and Bailey’s touring cabinet of curiosities. The sober staging and style seemed to invite viewers to...
forces with genuine laboratories with animal facilities, an aquarium, a vivarium, biology, chemistry, and physics departments, their films acquired an educational purpose. Some 450 one-reelers popularizing science were produced in the four years before the war. To kindle the interest of younger viewers and to overcome any mind-wandering, the films showed odd or unfamiliar creatures and insects. The industrialist Charles Pathé was convinced of their educational value, saying that “the cinematograph will be the theater, newspaper, and school of tomorrow.” Édouard Petit, the chief inspector of schools, begged to differ, believing that in the cinema “the somewhat rushed sequence of images deforms the slow and progressive work of nature.”

To adapt to the large variations in the duration of natural or biological phenomena, the scientific film from the outset used techniques that would later be adopted by those making films for cinematic storytelling: slow motion and time-lapse photography. One of Marey’s collaborators, the photographer Lucien Bull, originated high-speed cameras which, in the early 1900s, filmed at 1200 and then 4000 images per second, and over the years he refined them until by 1951 they could record one million images per second. Bull also invented a camera for microcinematography capable of 8- to 10-fold magnification.

Interest in scientific films waned at the start of the First World War and laboratories were dismantled and their staff laid off. Scientific documentaries took their place, but were less popular and designed for a different purpose: the dissemination of scientific knowledge to prepared minds and the creation of audiences keen on this type of film.

Using itinerant film shows to teach public hygiene

In 1917, as the United States of America joined forces with the Allies in World War I, the Rockefeller Foundation sent a commission to France “to aid that country in organizing a fight...
upon tuberculosis, by which under existing conditions the population was seriously menaced.” The Commission for the Prevention of Tuberculosis in France was solemnly welcomed by French President Raymond Poincaré on 9 August 1917. It was funded by The Rockefeller Foundation to the tune of $522,459 (the equivalent today of roughly 45 million euros), and included training courses for doctors and health visitors, the running of dispensaries throughout France (70% of the population lived in rural areas), and “a campaign of popular education by means of traveling exhibits, lectures, slides, moving pictures, posters, pamphlets, and press articles.” Five circulating educational units known as the “roulottes d’hygiène” (hygiene caravans) traveled the length and breadth of France. Aboard each were an electrical generator, film projection equipment, films, documents, 42 exhibition posters, and five people: the (American) film director, a female lecturer, a male lecturer, a mailman, and a “driver-cinematographer.”

Public health propaganda using moving pictures spread in France during World War I after the setting up of an extra-parliamentary commission to study how to extend the use of cinematography to other areas of teaching. Most films shown by the Rockefeller mission, some 150 in all, were produced by Pathé and by Gaumont. Their titles left little to the imagination: Don’t Spit on the Ground, Beware the Fly, Don’t Lick your Fingers to Turn the Page, The Slums Must be Vanquished, Fingernails in Mourning. These and like films were aimed at teachers and university lecturers, the middle classes, soldiers, housewives, and workers. And above all children, for whom the Rockefeller lecturers ran “health crusades” with the added incentive of prizes. Between 1917 and 1922, the Rockefeller mission organized 6800 talks, distributed 15 million leaflets, and launched extensive American-style press campaigns. Close to three million French people attended the talks and lectures. After World War I, public health education using films continued, notably in the fight against tuberculosis through the National Committee for Defense Against Tuberculosis (which took over the films of the Rockefeller mission). The task of making new films was entrusted to Jean Benoît-Lévy, who between 1920 and 1944 made to order for various governmental ministries almost 300 one-reelers and 15 features. These scientific and educational films were made in consultation with medical officers, notably Dr Louis Devraigne, head of the maternity ward at the Lariboisière Hospital in Paris, who gave advice (and provided scripts). In 1927 alone ten million French people attended these film shows, which were the educational medium most popular with the working classes and rural populations.

Designed to appeal to, and so to educate, the general public, Benoît-Lévy’s films extolled the values of humanism and of republican science. Produced by the Société d’édition cinématographique française, which Benoît-Lévy created in 1922, there were films on cancer, the prevention of syphilis, and alcoholism. The first great film recounted the life and work of Louis Pasteur. Others followed, like The Mother-To-Be on infant care, The Sacred Veil on visiting nurses, and Maternity, which advocated a pro-birth policy.

In a December 1932 interview, Benoît-Lévy spoke of his belief that educational films have much in common, and oftentimes are confused, with drama films, from which they borrow ideas on how to be more compelling. Benoît-Lévy felt...
that educational films fall into two clearly distinct genres: those used to illustrate a talk and to transmit understanding, and those shown in ordinary film theaters and intended to appeal to heart and soul. Education, Benoît-Lévy believed, speaks above all to the intellect in the first genre, and to the sentiments in the second, provided, that is, mind and heart can be partitioned so neatly.12,14

Making the transition to the talkies, Benoît-Lévy produced two realistic films—Itto and Hélène—in which the image of the rebellious woman, mistress of her own destiny, contrasted sharply with the silent images of Maternity.12 He also made films for the teaching of surgery, as part of a medical-surgical cinematographic encyclopedia, a project curtailed by the outbreak of war in 1939.

A new genre: the independent science documentary
Dr Jean Comandon “filmed the invisible.” A maker of scientific films before World War I, Comandon later moved on to documentaries. His research on microcinematography at the Saint Louis Hospital in Paris was given technical backup by Pathé, which he joined in 1906 to work its laboratory. There he made films like Crystallization, The Curious Soldier Flies: The Stratiomyidae, and The Movement of Plants.

Beset by financial difficulties, Pathé stopped producing scientific films in 1926 and closed the laboratory where Comandon worked. Already the recipient of various distinctions and awards for his work, Comandon set up a scientific cinematography lab at the Institut Pasteur in Garches (near Paris) where he made films like The Phagocytosis of Trypanosomes by White Blood Cells and The Circulation of Blood.15,16

In the 1920s, film clubs, educational cinema offices, and specialized projection rooms ensured the survival of scientific cinema in a new form where mostly documentary films were shown to the public. Jean Painlevé bestrode French scientific cinema of the 1920s. Biologist, scriptwriter, friend of the surrealists, humanist, jewelry designer, racing car driv-

Painlevé was friends with renowned film directors like Jacques Prévert, Henri Langlois, Georges Franju, Sergei Eisenstein, Luis Buñuel, Jean Vigo, and Abel Gance. He used musicians in the making of his documentaries like *L’Hippocampe*, for which Darius Milhaud wrote the music, and in *The Vampire*, in which the life of a vampire bat was illustrated by the music of Duke Ellington, including *Echoes of the Jungle* (Painlevé was a jazz pianist too!).

In all, Painlevé took part in the making of almost 200 films, using the latest technologies: underwater filming, special effects, steadycam. In 1930, he made a militant four-minute film in which he declared his support for the use of citrate in anticoagulation to stem massive bleeding, as recommended by a physician with the rank of general in the French military, but recently refused by the French Defense Health Service Authorities.17,18 Dr Pierre Thévenard started his career as a film scientific director in 1934 by making 35-mm films on urologic surgery and followed this up with an uninterrupted series of science documentaries and films, some of which won awards: *Beware of Vipers*, *Ultrasound*, *The Killer Mushroom*, *The True Culprit*, a drama commissioned by the French welfare system to warn of the dangers of induced abortion, *The Question of Cancer*, an encyclopedic review in thirteen reels, and *The Adventures of a Bluebottle*. A good number of Thévenard’s films were set to music by André Jolivet, while popular actors and members of the Comédie-Française did the voiceovers. After Thévenard joined the scientific cinematography laboratory of the Institut Pasteur, he was commissioned to make a documentary on Albert Calmette, co-discoverer of the bacillus Calmette-Guérin, used in vaccination against tuberculosis. This and other films brought Thévenard international renown.8,19

In the early 20th century, a visit to the newfangled cinema was a risky affair. Eighteen-year-old Miss R. of Bordeaux paid for her cinematic passion with conjunctivitis after every show. And M. C., a barber of that same French city, was unable to read his newspaper for days after every visit to a film theater. What was happening? In 1909, local ophthalmologist Dr Ginestous provided the answer when he gave a paper on a new medical phenomenon he had discovered: “cinemophthalmia.”

Cinemophthalmia had several clinical variants: simple eye watering with photophobia, inflammatory erythema of the eyelids and of the conjunctiva, problems focusing, exhaustion of ocular reflexes, notably fatigue of the internal eye muscles, and retinal asthenopia without loss of visual acuity or abnormal refraction. Despite this alarming list of disorders, Dr Ginestous sought to hearten, saying that in fact ophthalmias of this type had a good prognosis and usually resolved quickly, even without treatment. As for prophylaxis, Dr Ginestous had the answers: choose a better class of film theater where they use new reels of film (no slippage) and the correct projection speed; wear blue-tinted glasses; peer at the screen through fanned fingers or fibrous palm leaves; use eyedrops containing cocaine or adrenaline.

Cinemophthalmia receded after World War I, like a fading retinal image, pushed into a footnote on the history of medicine by improvements in cinema projection equipment, filming techniques, and celluloid film.21-24

**“Cinemophthalmia,” the bane of early cinemagoers**

In the early years of cinematography, the persistence of luminous impressions on the retina was calculated to last 2/25 of a second, and so filmmakers adopted a projection speed of 16 images/second for 35-mm film. To produce the cinematographic illusion, the succeeding images must remain superimposed on the retina for long enough to give the impression of movement. Each projected image requires an illumination phase and a phase during which the film is advanced at a fixed speed by one frame. The resulting scintillation of the image generated eye strain, particularly as knavish film theater directors tended to slow the projection speed so as to lengthen the show: a 1000-meter film lasted 54 minutes when projected at 16 images/second and 62 minutes at 14 images/second. This new ailment of cinemophthalmia discovered by Dr Ginestous was believed to be triggered by the poor quality of films, which were stained and scratched, by celluloid of uneven thickness and grain, by poor shots dotted with fuzzy and indistinct details that force the viewer’s eye constantly to change focus (accommodation), and by deterioration of the film perforations resulting in slippage of the film.
Epilogue

Movies have long depicted stories of medical practitioners in a bewildering array of guises: the hospital bigwig, a country doctor, a physician and humanist, the doomed hero, the consumptive condemned to a slow death, loathsome mishapenness and disfigurement, the chilling diagnosis of cancer, traumatic childbirth. The sick and the lame have served as a mirror, a concept, a vehicle for a social conception of disease and suffering.20

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Because Langlois considered film images as reflecting how people dressed, moved, ate, entertained themselves—in short lived—at a particular time and place, determining how those coming after it would view it, he viewed every frame as testimony. His motto was “Everything must be saved.” It was thanks to him that the work of the Lumière brothers and Georges Méliès was rescued from oblivion, that pre-War cinema has been handed down to posterity, and that the French New Wave was made possible.

As with film institutes or “cinematheques” the world over, the vocation of the Cinémathèque, founded in Paris in 1936, was to preserve, restore, research, and show films, playing the same role for the moving image as libraries for books or museums for paintings. That the Cinémathèque is perhaps the best endowed of its kind, holding around 40,000 films, is largely down to one man, Henri Langlois. Born in Izmir in 1914 and a devotee of film from childhood, Langlois founded a silent film preservation club in Paris in 1935. A year later, aged 22, he became the first director of the Cinémathèque, which he and two friends set up to save and preserve every film wherever made, whether masterpiece or middling. His ambition also extended to rescuing from oblivion anything related to film, including scenarios, sets, costumes, and projectors. Larger than life, a law unto himself—the archetypal sacred monster—Henri Langlois let nothing stand between himself and film. During the Second World War and the Occupation, he saved the Cinémathèque’s collection from destruction. His obsession was his strength. He forged close friendships with Chaplin and Hitchcock, and encouraged New Wave directors on both sides of the Atlantic. As the soul and archeologist of the moving image, he was for the poet Jean Cocteau the “dragon standing guard over our treasure,” all of which is now on exhibition in the rejuvenated 12th arrondissement of Paris to the delectation of modern movie-lovers.

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have seen had not Langlois, “driven” (Truffaut) by his mono-
maniacal obsession, spent his days, nights, and entire life at-
ttempting to preserve everything that had been filmed since
images were first made to move. Langlois was a larger than
life figure, a law unto himself—the archetypal sacred monster.
Had he not been obsessed by the urgent necessity of “saving
everything,” what would have become of the Lumière broth-
ers’ archive or the cinematic of Georges Méliès? Who, but for
him, would have seen Marlene Dietrich in The Blue Angel were
it not for its miraculous escape from destruction from Ger-
man wartime censorship? How else would France have been
introduced to Soviet cinema, Hollywood epics, and Japan-
ese masterpieces? Filmmakers the world over are indebted
to the “dragon,” as the poet Jean Cocteau called him, for
having been there to “stand guard” over the treasures of their
profession.

But Langlois was not content to track films down, identify
them, and show them. He also saw himself as an archeol-
ogist. His aim was to save everything and anything that was
related directly or indirectly to cinema, including scenarios, ob-
jects, costumes, sets, and projectors. His collection had more
than a hint of Ali Baba’s cave to it. But who else was able to
forge links of mutual respect and friendship so strong that
Charlie Chaplin himself donated part of the cogwheels from
Modern Times, Martine Carol the dresses she wore in Max
Ophuls’ Lola Montès, Louise Brooks the buckles from her
stage shoes, Fritz Lang the robot he dreamed up for Metro-
polis, or Alfred Hitchcock the death head of Anthony Perkins’
mother in Psycho, posted in a large cardboard box?

“Our spiritual home”
When the Cinémathèque left the Palais de Chaillot and moved
to the new quarters in the 12th arrondissement, in a build-
ing designed by Frank Gehry, Martin Scorsese declared at
the opening: “Filmmakers the world over are familiar with the
French Cinémathèque, even if they have never been here.
It’s our spiritual home.”
This moving testimony reflected the reputation of an institution brought into being in 1936 by three devotees of what in France is commonly referred to as the seventh art: director Georges Franju (1912-1987), film critic Jean Mitry (1907-1988), and Henri Langlois (1914-1977).

Franju and Langlois had met in the early '30s at a printer’s where the young Langlois had been apprenticed by his father after failing his exams. Born in Izmir, ex-Smyrna, in 1914 to French parents forced to return to France after the Greek city was taken by Turkey in 1922, Henri Langlois had only one interest: cinema. It was the one and only passion in his life, to the extent that he chose to go to the movies rather than sit for his baccalaureat, to the great despair of his father. Franju and Langlois found themselves partners in the same passion.

Together they borrowed 500 francs (equivalent to 375 euros in 2013 [INSEE indicator]) from Henri’s parents to set up a sort of film club, Le Cercle du Cinéma (The Cinema Circle), where they showed silent films, encouraged by the film historian Jean Mitry who was convinced that the advent of the talkies would condemn the masterpieces of silent cinema to oblivion if nobody bothered to preserve the reels. There was no institution of any kind devoted to the protec-
tion or preservation of what was yet to be acknowledged as the seventh art. The founding principle of the Cinémathèque was the desire to preserve a heritage under threat. Barely 22, yet already steeped in film history and culture, there was no one more fitting to preside over such an institution than Henri Langlois.

His ambition was to preserve everything: the good along with the not so good, final cuts along with outtakes. He excluded nothing: scale models, scenarios, stills, sets, costumes, projectors, etc. Langlois was the first to look beyond, or beneath, the masterpieces of cinema and take an interest in all films. He saved everything, even the stinkers. Bad films too are a record of their time. That is what drove Langlois. “I wanted the shades of the living to mingle with those of the dead,” said Langlois in justifying his approach under the triple guise of archeologist, sociologist, and historian, “because that is what cinema is about.”

“Everything must be saved”
Because Langlois considered film images as reflecting how people dressed, moved, ate, entertained themselves—in short lived—at a particular time and place, determining how those coming after it would view it, he viewed every frame as testimony. His motto was “Everything must be saved.” It was thanks to him that the work of the Lumière brothers and Georges Méliès was rescued from oblivion, that pre-War cinema has been handed down to posterity, and that the French New Wave was made possible.

The Cinémathèque’s first home, like its current home, was in the 12th arrondissement, but in the rue Marsoulan. From the start it was designed as both museum and cinema. Langlois had the appetite of an ogre. He increased the Cinémathèque’s archive from ten films in 1936 to over 60,000 in 1970. But if anything he was even keener to show them. Langlois saved films by recovering them, but also by restoring them when they had begun to decompose. Most were made of celluloid, a fragile material that disintegrates under adverse storage conditions.
The Cinémathèque was built on the donation of films by filmmakers and producers thanks to a relationship with Langlois based on mutual gratitude and admiration. Langlois was able to show the films without paying fees, but they remained the property of those who entrusted them with him. Perhaps the bulk of the collection belonged to Langlois himself, a compulsive collector and inspired flea-market trawler, who was snapping up items long before governments recognized the need to establish cinematographic archives.

Americans in particular were grateful to the Cinémathèque’s director for having preserved works that would no longer have existed without his intervention. It is thanks to Langlois, for instance, that we still have Abel Gance’s magnificent Napoleon (1927), one of the masterpieces of silent cinema. The German Occupation deprived the Cinémathèque of a home of its own. To get round the censor, Langlois organized clandestine viewings at his mother’s, attended in particular by Simone Signoret, who had no hesitation, despite her Polish-Jewish father, in crossing Paris under the Occupier’s nose pushing a pram full of reels. “The first time I saw Battleship Potemkin,” remembered Signoret, “was in 1941, rue Troyon, in the dining room at Langlois’ mother’s. All the Soviet films, and all the films by Renoir or Prévert that were banned under the Occupation, in fact the only great films that I saw during this period, were shown to me by Langlois who used to carry his reels around in the métro. It sounds funny now, but at the time it was dangerous.” Without Langlois and his daring ingenuity, Robert Wiene’s The Cabinet of Dr Cagliari (1919), or Georges Méliès’ Joan of Arc (1900), or Josef von Sternberg’s The Blue Angel with Marlene Dietrich, to take but three examples, would have been lost to history. Many items in the Cinémathèque archive were under threat during the Occupation, and Langlois managed to hide them by secreting his films in any number of hiding places in Paris, burying some in Michel Simon’s garden, and hiding others—those by Chaplin and Soviet directors—in a Bordeaux wine estate. By 1944, Langlois had saved 40,000 films. As soon as the War ended he set out to find a home for them.

The small theater on the rue de Messine
In 1948, he found premises at 8 rue de Messine, near the Champs-Elysées. Keeping to the same fundamentals: “preserve and show,” he decided to show only once. The single-showing idea was simple, and caught on. It was the key to his success.

Hungry to catch the one-off showings of Langlois’ rare finds, cinephiles were assiduous in their attendance, meeting up for each week’s program of unmissable films that Langlois used to stencil on a single sheet of paper. They included the...
young Claude Chabrol, François Truffaut, Eric Rohmer, Jean-Luc Godard, Alain Resnais, Jacques Rivette, and others, all irrevocably committed to film, with Langlois as their spiritual godfather. It’s thanks to Langlois that they saw their first undubbed Japanese film and their first Buster Keaton (subtitled in Czech…). It was Langlois who trained and sharpened their eye. “Enjoying cinema,” Langlois used to say, “means enjoying life.”

Competition was fierce for the sixty seats of the little theater on the rue de Messine. Jean-Paul Sartre and Simone de Beauvoir were regulars, as were André Gide, Georges Braque, Fernand Léger, and the future French president Georges Pompidou. After each showing discussion would go on for hours in the street outside as Langlois had no time for the staged dissection of films after they were shown. Langlois did not only rescue riches from the past. He also celebrated, made known and encouraged the directors of the future, such as the French New Wave, the violently controversial Rainer Werner Fassbinder, and Nicholas Ray, one of the leading post-War Hollywood directors (Johnny Guitar, 1954, and Rebel Without a Cause, 1955, with James Dean). “The work by the French Cinémathèque was without doubt the most important individual effort in cinema history,” said Ray in support of Langlois in February ‘68.

A man “driven”
Langlois was characterful to have only attracted admirers. His detractors accused him of being muddle-headed, a hopeless manager, and a thief to boot. Langlois behaved like a scavenger, with the ethics and clothing to match. He was accused of keeping negatives any old how, of letting reels rust in his bath (a rumor which only compounded his unwashed image), and of alarming nontransparency as to both the precise methods by which he acquired some of the items in his collection or their exact location. He was shielded by a close guard of volunteers who were prepared, like Langlois himself, for any sacrifice that would enrich or protect his collection, especially as they were convinced that the whole world was out to wrest them from him. The renowned film critic Serge Daney sketched a realistic portrait of the “poet of film”: “Like all driven men, Henri Langlois divided the world, people and events into two blocks: 1. Those that were good for the Cinémathèque. 2. Those that were not good for the Cinémathèque. Even if he’d known you for ten years, he didn’t waste time asking after your health or your family because the very notions of health or family only had meaning in terms of the health of the Cinémathèque or the family of the Cinémathèque.

That didn’t stop him being warm, provided you agreed to board the train of his conversation, which was more exactly a conspiracy-centered monologue”—the conspiracy being the constant threat of a State stranglehold over his collection.

Langlois was paranoid. But he was not mad. He knew that the Cinémathèque had outgrown the era of heroic one-man effort. Its riches had become an incitement to State lust. André Malraux, the then Minister of Culture, made a first attempt at modifying the status and management of the Cinémathèque in 1963, more exactly to convert it from a private association to a fully State-funded institution. In exchange for State support, a theater in the Palais de Chaillot, and increased funding, Malraux wanted a leading role on the board of directors and the power to appoint a regular and dependable financial officer. In February 1968, Malraux stopped beating about the bush: he dismissed Langlois.

World cinema takes to the street
The events of May ‘68, when the country rose up against a deaf and authoritarian government, were only weeks away, and Malraux underestimated the stature and loyalty of the troops at Langlois’ command. Indeed, so spontaneous was the loyalty that command was unnecessary. Within twenty-four hours, world cinema had taken to the street: Abel Gance, François Truffaut, Jean-Luc Godard, Jean Renoir, and Robert Bresson banned the State from showing their films. They were joined by dozens of other filmmakers, including Charlie Chaplin, Roberto Rossellini, Fritz Lang, Richard Lester, Carl Dreyer, Orson Welles, and Jerry Lewis. Three thousand people demonstrated outside the Palais de Chaillot. The police charged. Godard was wounded, and François Truffaut used scenes
from the demonstration in Stolen Kisses, which he dedicated to the Cinémathèque when it came out the following year. There were riots outside the Cinémathèque offices in the rue de Courcelles. A petition gathered 700 signatures from the international cinematographic elite: the directors Michelangelo Antonioni, Ingmar Bergman, Luis Buñuel, Peter Brook, Alfred Hitchcock, Elia Kazan, Akira Kurosawa, Pier Paolo Pasolini, Claude Berri, Satyajit Ray, and Andy Warhol; actors such as Jean-Paul Belmondo, Brigitte Bardot, Catherine Deneuve, Michel Simon, Simone Signoret, Marlene Dietrich, Jane Fonda, Katharine Hepburn, Peter O’Toole, and Gloria Swanson; as well as writers, artists and philosophers, such as Roland Barthes, Samuel Beckett, Alexander Calder, Truman Capote, Max Ernst, Eugene Ionesco, Pablo Picasso, Paul Ricoeur, Jean-Paul Sartre, Henri Cartier-Bresson, and Norman Mailer. The power of this Who’s Who of world culture was such that the government climbed down and Langlois could only be reinstated. He spent his remaining years on his singular creation, leaving behind him a Cinémathèque envied by the rest of the world.

The Cinémathèque was duly rescued from the jaws of the State, but paid for it by having its subsidies reduced to a minimum. Langlois fought to the end of his life to maintain his artistic ideal: a film museum designed to turn people into filmmakers rather than to satisfy consumers. He always maintained that true cinema was made by mauvais élèves, “bad pupils” who refuse to sit dutifully at their desks swallowing the teacher’s curricu-
lum. Once an ardent defender of the sacred monster, Truffaut eventually moved away, finding it increasingly difficult to tolerate Langlois’ ever more autocratic behavior and his tendency to show “commercial” films to bring in much-needed cash. In 1974, Henri Langlois received an honorary Oscar for his contribution to cinema. He and his wife Mary Meerson managed to keep the Cinémathèque afloat by dint of round-the-clock work. After his death on January 13 1977, his friends clubbed together to build a fitting monument over his grave in the Montparnasse cemetery—a sloping slab that reproduces scenes from iconic films.

From dormancy to rebirth
Bereft of its creator, the Cinémathèque and Museum of Cinema entered a dark period of semi-dormancy lasting two decades compounded in 1997 by a fire and the subsequent flood caused by the firemen’s hoses directed onto the roof of the Palais de Chaillot. The collections were saved, but the Cinémathèque found itself confined to a little theater on the Grands Boulevards until it was reborn and rehoused in 2005 in the building designed by Frank Gehry.

Our turn now to push open the door of this reincarnation. We find a Cinémathèque that has modern technologies to help it fulfill its timeless mission: to preserve and put on films, run the great classics, but also organize retrospectives and festivals dedicated to specific filmmakers, actors, producers, and technicians, archive the collections, display some of the fabulous objects in the museum, mount temporary exhibitions to give glimpses into the wealth of its holdings, and reinforce the links between film and the other arts. The Cinémathèque also has a library and archive at the disposal of students and...
researchers. After its record 300,000 visitors in the summer of 2012 for the temporary exhibition on the director Tim Burton, with over 500 drawings, photographs, and scale models, the Cinémathèque staged an exhibition in honor of Marcel Carné, another monument in the history of film. Generations of cinephiles were raised on Carné’s cult film, *Children of Paradise* (1945), which has since been re-released in theaters and on DVD. It was made under pressure during the German Occupation by those who—like the film’s writer Jacques Prévert and the actors Jean-Louis Barrault, Arletty, and Pierre Brasseur—were out to prove that the French spirit was still free even if France itself was not, much as Langlois always remained a free spirit even when his Cinémathèque appeared threatened by chains.

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Sunday 10 AM to 8 PM

www.cinematheque.fr

*Paris burning? Raging flames engulf the Palais de Chaillot on 22 July 1997, threatening to destruct the collections of the Cinémathèque. © AFP.*

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